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Chlorinated Phenols: Ambient Water Quality Criteria

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for chlorinated phenols. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi. . . .

KEYWORDS: *Water quality, *Toxicology, *Phenols, *Chlorine organic compounds, *Toxic substances, *Water pollution effects(Humans).

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CHLORINATED PHENOLS

Ambient Water Quality Criteria

Criteria and Standards Division
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Washington, D.C.

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CRITERION DOCUMENT

CHLORINATED PHENOLS

CRITERIA

Aquatic Life

For 4-chlorophenol the criterion to protect freshwater aquatic life as derived using the Guidelines is 45 ug/l as a 24-hour average and the concentration should not exceed 180 ug/l at any time.

For 2,4,6-trichlorophenol the criterion to protect freshwater aquatic life as derived using the Guidelines is 52 ug/l as a 24-hour average and the concentration should not exceed 150 ug/l at any time.

For saltwater aquatic life, no criterion for any chlorinated phenol can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the prevention of adverse effects due to the organoleptic or toxic properties of chlorinated phenols in water, the following criteria are recommended:

Monochlorophenols	
3-chlorophenol	50 ug/l
4-chlorophenol	30 ug/l
Dichlorophenol	
2,5-dichlorophenol	3.0 ug/l
2,6-dichlorophenol	3.0 ug/l
Trichlorophenol	
2,4,5-trichlorophenol	10 ug/l
2,4,6-trichlorophenol	100 ug/l

Tetrachlorophenol*

2,3,4,6-tetrachlorophenol   263 μg/l

Chlorocresol

Insufficient Data

*This criterion is based on toxicological effects; all other criterion are based on organoleptic effects.

CHLORINATED PHENOLS

Introduction

The chlorinated phenols represent a group of commercially produced, substituted phenols and cresols referred to as chlorophenols and chlorocresols. Chlorinated phenols are used as intermediates in the synthesis of dyes, pigments, phenolic resins, pesticides, and herbicides. Certain chlorophenols also are used directly as flea repellants, fungicides, wood preservatives, mold inhibitors, antiseptics, disinfectants, and antigumming agents for gasoline. (The compounds 2-chlorophenol, 2,4-dichlorophenol and pentachlorophenol are discussed in separate criteria documents.)

The chlorinated phenols represent a group of substituted phenols and cresols prepared by direct chlorination or the hydrolysis of the higher chlorinated derivatives of benzene. Purified chlorinated phenols exist as colorless crystaline solids, with the exception of 2-chlorophenol which is a clear liquid, while the technical grades may be light tan or slightly pink due to impurities (Bennett, 1962; Kirk and Othmer, 1963; Heilbron, et al. 1946-75; Sax, 1975; Weast, 1974; Windholz, 1976; Hawley, 1975). As a group, the chlorophenols are characterized by an odor which has been described as unpleasant, medicinal, pungent, phenolic, strong, or persistent (Kirk and Othmer, 1963; Sax, 1975; Lange, 1952).

A summary of the various pertinent physical properties is presented in Table 1. In general, the volatility of the compounds decreases and the melting and boiling points increase as the number of substituted chlorine atoms increases.

TABLE 1

Physical Properties of Chlorinated Phenols

Compound	MW	pK	MP (deg. C)	BP (deg. C)	Density	Water sol. (g/100g)*	Vapor pressure (mm Hg/ deg. C)
Chlorophenols							
2-	128.56	8.48	8.7	175	1.2634	0.1-2.85	1/12.1
3-	128.56	9.08	33.	214	1.2680	0.26	1/12.1
4-	128.56	9.42	43.2	219	1.2651	2.71	
2,3-di-	163	7.70	57.	206	---	---	
2,4-di-	163.	7.85	45.	210	1.3830	sl.	
2,5-di-	163.	7.51	58.	212	---	sl.	
2,6-di-	163.	6.79	67.	219	---	---	1/59.5
3,4-di-	163.	8.59	68.	253	---	sl.	
3,5-di-	163.	8.19	68	233	---	s.	
2,3,4-tri	197.5	---	83.5	Sublimes	---	---	
2,3,5-tri-	197.5	---	62	255	---	s.	
2,3,6-tri-	197.5	---	58	272	1.4901	sl.	
2,4,5-tri	197.5	7.0	68	245	---	0.2	1/72.0
2,4,6-tri-	197.5	6.1	69.5	246	---	0.1	1/76.5
2,3,4,5-tetra-	232.	---	116.	Sublimes	1.6700	---	
2,3,5,6-tetra-	232.	5.3	115.	---	---	0.1	
Pentachlorophenol	266.35	4.8	190-191	309-310	1.9780	0.0014	
Chloro-o-cresols							
3-	142.55	---	86.	225	---	sl.	
4-	142.59	---	51.	223	---	sl.	
5-	142.59	---	73.	---	---	---	
6-	142.59	---	---	118	---	sl.	
4,5-di-	177.03	---	101.	---	---	sl.	
4,6-di-	177.03	---	55.	266.5	---	sl.	
3,4,5-di-	177.03	---	101.	---	---	sl.	
3,4,6-di-	177.03	---	55.	226	---	sl.	
3,4,6-tri-	211.5	---	62.	---	---	---	
4,5,6-tri-	211.5	---	77.	269	---	sl.	
3,4,5,6-tetra-	245.9	---	190.	---	---	---	

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* sl. - slightly soluble, s. - soluble

TABLE 1 (contd.)

Physical Properties of Chlorinated Phenols

Compound	MW	pK	MP (deg. C)	BP (deg. C)	Density	Water sol. (g/100g)	Vapor pressure (mm Hg/ deg. C)
Chloro-m-cresols							
2-	142.59	---	55.	196	---	sl.	
4-	142.59	---	66.	235	---	0.38	
6-	142.59	---	45.	196	---	s.	
2,4-di-	177.03	---	27.	241	---	---	
2,6-di-	177.03	---	58.	235	---	---	
4,6-di-	177.03	---	72.	235	---	---	
2,4,6-tri-	211.48	---	45.	265	---	sl.	
2,4,5,6-tetra-	252.9	---	189.	---	---	s.	
Chloro-p-cresols							
2-	142.59	---	195.	---	---	sl.	
3-	142.59	---	55.	228	---	s.	
2,6-di-	177.03	---	39.	138	---	sl.	
2,3,5,6-tetra-	245.42	---	190.	---	---	---	

References:
1. Bennett, 1962
2. Kirk and Othmer, 1963
3. Heilbron, 1946
4. Weast, 1978
5. Sax, 1975
6. Weast, 1974
7. Windholz, 1976
8. Pearce & Simkins, 1968

The solubility of the chlorophenols and chlorocresols, with the exception of 2,4,6-trichloro-m-cresol, range from soluble to very soluble in relatively non-polar solvents such as benzene and petroleum ether. Although chlorophenols are considered weak acids, they are stronger acids than phenol and can be converted to the corresponding phenoxide salt by various bases including soduim carbonate. The dissociation constants (pKa) for the chlorinated phenols progressively decrease with increased substitution of chlorine atoms into the aromatic ring. Although the solubility of chlorinated phenols in aqueous solutions is relatively low, it increases markedly when the pH of the solution exceeds the specific pKa, since the more readily soluble phenoxide salt is formed. The phenoxide salts are also more soluble than the corresponding phenol in water and neutral pH.

A summary of the methods of synthesis and principal uses of the commercially most important chlorinated phenols is presented in Table 2. Since the hydroxyl group of the phenol molecule exerts a relatively strong ortho-, para-directing influence over the electrophylic substitution of chlorine atoms, the compounds preferentially formed during the direct chlorination of phenol are 4-chlorophenol, 2-chlorophenol, 2,4-dichlorophenol, 2,6-dichlorophenol, 2,4,6-trichlorophenol, and 2,3,4,6-tetrachlorophenol. Other positional isomers may be synthesized by the hydrolysis of higher chlorobenzenes. Many of the chlorinated phenols have no commercial application presently due to their high cost of production, complex synthetic procedures, or lack of useful chemical, physical, or toxicological properties (Kirk and Othmer,

TABLE 2

Summary of the Synthesis and Uses of Various chlorinated Phenols

Chlorinated Phenol	Method of Synthesis	Principal Uses	References
4-chlorophenol (4-CP)	Direct chlorination of phenol	To produce 2,4-DCP, and a germicide 4-chlorophenol-o-cresol	Kirk & Othmer, 1964
2,4-dichlorophenol (2,4-DCP)	Direct chlorination of phenol	To produce herbicide 2,4-D, also a mothproofing cpd., an antiseptic and a miticide	U.S. EPA, 1973 Kirk & Othmer, 1964
2,4,5-trichlorophenol (2,4,5-TCP)	Hydrolysis of 1,2,4,5-tetrachlorobenzene	To produce defoliant 2,4,5-T and related products. Also used directly as a fungicide, antimildew and preservative agent, algicide, bactericide	U.S. EPA, 1973, Kirk & Othmer, 1964
2,4,6-trichlorophenol (2,4,6-TCP)	Direct chlorination of phenol	To produce 2,3,4,6-TCP and PCP. Used directly as germicide, bactericide, glue and wood preservative and antimildew treatment	U.S. EPA, 1973, Kirk & Othmer, 1964
2,3,4,6-tetrachlorophenol (2,3,4,6-TCP)	Direct chlorination of phenol or lower chlorophenols	Used directly as bactericide, fungicide, insecticide, wood and leather preservative	U.S. EPA, 1973 Kirk & Othmer, 1964
Pentachlorophenol (PCP)	Direct chlorination of phenol or lower phenols	Used directly as a wood preservative, herbicide, insecticide and moluscicide	Kirk & Othmer, 1964
4-chloro-o-cresol (4-c-o-c)	Direct chlorination of o-cresol	To produce the herbicide MCPA	U.S. EPA, 1973, Kirk & Othmer, 1964

1963). These include 3-chlorophenol, 2,3-dichlorophenol., 2,5-dichlorophenol, 3,4-dichlorophenol, 3,5-dichlorophenol, 2,3,4-trichlorophenol, 2,3,5-trichlorophenol, 2,3,4,5-tetrachlorophenol, and 2,3,5,6-tetrachlorophenol. However, each of these compounds is produced to some extent as a byproduct during the production of the commercially important chlorophenols. From a commercial standpoint, 4-chloro-o-cresol is the most important of the chlorinated cresols (Kirk and Othmer, 1963).

It is well known that the highly toxic polychlorinated dibenzo-p-dioxins may be formed during the chemical synthesis of some chlorophenols and that the amount of contaminant formed is dependent upon the temperature and pressure control of the reaction (Fishbein, 1973; Milnes, 1971; Schulz, 1968; Higginbotham, et al. 1968; Muelder and Shadoff, 1973). The toxicity of the dioxins varies with the position and number of substituted chlorined atoms and those containing chlorine in the 2,3 and 7 positions are particularly toxic (Burger, 1973). The 2,3,7,8-tetrachloridibenzo-p-dioxin (TCDD) is considered the most toxic of all the dioxins (Sparschu, et al. 1971).

TCDD is apparently formed during the synthesis of 2,4,5-trichlorophenol and before 1968 was reported to be present in the subsequent product 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) at levels up to 10 mg/kg (Kearney, et al. 1973; Fishbein, 1973). By 1971 TCDD levels in commercial 2,4,5-T were below 1 mg/kg (Greig, et al. 1973; Hussain, et al. 1972) and are currently reported to be below 0.099

mg/kg (Dow, 1977). These TCDD levels are below the limit of 0.1 mg/kg recommended to the U.S. Environmental Protection Agency Administrator on May 7, 1971 by the Advisory Committee.

No TCDD was reported present in samples of commercial grade tetrachlorophenol although 28, 80, and 30 mg/kg of the hexachloro, heptachloro-, and octachlorodibenzo-p-dioxins and 55, 100, and 25 mg/kg of the hexachloro-heptachloro, and octachlorodibenzofurans were present, respectively (Schwetz, et al. 1974a). No TCDD has been reported present in commercial pentachlorophenol products although hexa-, hepta-, and octo-chlorodibenzo-p-dioxins have been detected at concentrations of 4 to 27 mg/kg, 125 mg/kg, and 50 to 2,510 mg/kg, respectively (Johnson, et al. 1973; Jensen and Reuberg, 1973; Schwetz, et al. 1974b).

Evidence has accumulated that the various chlorophenols are formed as intermediate metabolites during the microbiological degradation of the herbicides 2,4-D and 2,4,5-T and pesticides sivex, ronnel, lindane, and benzene hexachloride (Kearney and Kaufman, 1972; Steenson and Walker, 1957; Fernley and Evans, 1959; Loos, et al. 1967; Aly and Faust, 1964; Crosby and Tutass, 1966; Watts and Stonherr, 1973; Crosby and Wong, 1973; Goto, et al. 1972; Leng, 1976). In veiw of the information presented, it is clear that chlorinated phenols represent important compounds with regard to potential point source and non-point source water contamination.

Chlorophenols may be produced inadvertently by chlorination reactions which take place during the disinfection of waste water effluents or drinking water sources. Phenol has been reported to be highly reactive to chlorine in dilute aqueous solutions over a considerable pH range (Carlson and Caple, 1975; Middaugh and Davis, 1976). The formation of 2- and 4-chlorophenol and higher phenols has been reported under conditions similar to those employed during the disinfection of waste water effluents (Aly, 1968; Barnhart and Campbell, 1972) and the synthesis of 2-chlorophenol took place in 1 hour in aqueous solutions containing as little as 10 mg/l phenol and 20 mg/l chlorine (Barnhart and Campbell, 1972). Other studies have demonstrated the formation of up to 1.7 µg/l 2-chlorophenol during the chlorination of sewage effluents and cooling tower waters (Jolly, 1973; Jolly, et al. 1975).

Limited data are available on levels of chlorinated phenols present in industrial and municipal wastes, natural waters, drinking waters, or soils and sediments. 3-Chlorophenol, 4-chlorophenol, and 4-chloro-3-methylphenol (4-chloro-m-cresol) have been identified in chlorinated samples of both primary and secondary effluents and pentachlorophenol was found in domestic sewage treatment effluents (U.S. EPA, 1975). However, no quatitative data were reported. Examples of some findings are: The presence of 2,4-dichlorophenol in a local water intake system at a concentration of 6.6 µg/l has been noted. Pentachlorophenol concentrations of 4.3 µg/l (1 to 5 µg/l range) in some sewage effluent have been reported. In another case a river used as a drinking water supply contained 0.10 to 0.70 µg/l pentachlorophenol with 40 percent of these levels retained in the finished drinking water. The presence of 10 to 18 mg/l pentachlorophenol was found in a study of a small stream near a wood preservation site with surface oil slicks containing 5,800 mg/l pentachlorophenol. In the same study, pentachlorophenol concentrations of 0.1 to 0.2 mg/l and 0.05 mg/l were found in samples take 1/2 mile and 2 miles downstream, respectively.

It is generally accepted that chlorinated phenols will undergo photolysis in aqueous solutions as a result of ultraviolet irradiation and that photodegradation leads to the substitution of hydroxyl groups in place of the chlorine atoms with subsequent polymer formation. Studies by Grabowski (1961) and Joscheck and Miller (1966) indicated that UV irradiation of 2-chlorophenol produced catechol and/or 2,2-dihydroxydiphenyl. Omura and Matsuura (1971) reported that UV irradiation (290 mu) of 2-chlorophenol produced a complex mixture of products, including a large quantity of resinous material while the photolysis of 3-chlorophenol produced a high yield of resorcinol. Photolysis of 2,4-dichlorophenol in dilute aqueous solutions at a peak wavelength of 253.7 mu was virtually complete within 2 to 40 minutes depending upon the pH (Aly and Faust, 1964).

Other studies have demonstrated that photodegradation of 2,4-dichlorophenol following 5 hours of daily solar irradiation for 10 days (Crosby and Tutass, 1966). They observed the formation of the intermediates 4-chlorocatechol and 1,2,4-benzenetriol. The principal product of degradation recovered was a dark brown residue tentatively identfied as a mixture of dechlorinated polyquinoids. Although it has been speculated that photolysis of chlorophenols may produce dibenzo-p-dioxins, no 2,3,7,8-tetrachlorodibenzo-p-dioxin was detected during the riboflavin-sensitized photooxidation of 2,4-dichlorophenol to tetrachlorinated diphenol ethers (Plimmer and Klingebiel, 1971). Pentachlorophenol was shown to undergo photochemical degradation in aqueous solutions by ultraviolet irradiation and sunlight, with the formation of several chlorinated benzoquinones, 2,4,5,6-tetrachlororesorcinol, and chloranilic acid (Mitchell, 1961; Hamadmad, 1967). Wong and Crosby (1977) reported the degradation by sunlight or UV light of dilute solutions (100 mg/l) of pentachlorophenol to lower chlorophenols, tetrachlorodihydroxy benzenes, and non-aromatic fragments such as dichloromaleic acid. Subsequent irradiation of the tetrachlorodiols produced hydroxylated trichlorobenzoquinones, trichlorodiols, dichloromaleic acid, and non-aromatic compounds. The irradiation of dichloromaleic acid produced chloride ions and carbon dioxide.

Microbial degradation of chlorophenols has been reported by numerous investigators. Loos, et al. (1967) demonstrated the complete dechlorination and aromatic ring degradation of 2-chloro-, 4-chloro-, and 2,4-dichlorophenol by 2,4-D-grown cells of an Arthobacter species isolated from silt loam. Evans, et al. (1971), reported the degradation of 2-chlorophenol by several Pseudomonas species isolated from soil. Nachtigall and Butler (1974), using a Warburg respirometric technique, observed the oxidation of all monochlorophenols, 2,4- and 2,6-dichlorophenol, and 2,4,6-trichlorophenol by Pseudomoas sp. obtained through enrichment of and isolation from activated sludge. Alexander and Aleem (1961) reported the resistance of 2,4,5-trichlorophenol to microbial decomposition by certain soil bacteria. They observed that compounds containing a meta-substituted chlorine atom (position 3 or 5) appeared to be more resistant to microbial degradation. Ingols, et al. (1966), reported the complete aromatic ring degradation of 2,4-dichloro- and 2,4,6-trichlorophenol within 5 days by microbial action of an acclimated sludge, while 2,5-dichlorophenol was degraded only 52 percent.

Conversely, the destruction of 2,3,4,6-tetrachlorophenol by numerous fungal species of *Aspergillus*, *Penicillium*, and *Scopulariopsis* obtained from broiler house litter has been reported (Gee and Peel, 1974). In the same study, the tetrachlorophenol was completely metabolized by a mixed bacterial suspension also isolated from the litter. Although Ingols, et al. (1966), observed no alteration of sodium pentachlorophenol (NaPCP) by activated sludge microbes after 4 days of incubation, Watanabe (1973) reported the growth of an isolated species of *Pseudomonas* from PCP-perfused culture samples using PCP as the sole carbon source.

Organoleptic properties manifest themselves in 2 forms; the ability of a compound to impart an odor to water, and to cause tainting in fish flesh as a result of exposure to chlorophenol contaminated water. The organoleptic properties of chlorophenols have undergone rather extensive investigation. The threshold levels of monochlorophenols causing odor in water have been reported to be as low as 0.33 to 2.0 µg/l for 2-chlorophenol (Hoak, 1957; Burttschell, et al. 1959), 100 to 1,000 µg/l for 3-chlorophenol (Hoak, 1957;

Campbell, et al. 1958; Ruchoft and Ettinger, 1947), and 33 to 1,000 ug/l for 4-chlorophenol (Hoak, 1957; Burttschell, et al. 1959; Ruchoft and Ettinger, 1947). Threshold odor levels in water have also been reported to be 0.65 to 20 ug/l for dichlorophenols, 11 to 1,000 ug/l for trichlorophenols, 915 to 47,000 ug/l for tetrachlorophenols, and 857 to 12,000 ug/l for pentachlorophenol (Hoak, 1957; Burttschell, et al. 1959; Kinney, 1960; Ruchoft and Ettinger, 1947). It is apparent that the odor threshold progressively increases with an increase in substituted chlorine atoms.

The odor threshold of the cresols in water has been reported to be 71 ug/l, 333 ug/l and 45.4 ug/l for o-, m-, p-cresol, respectively, while the odor thresholds of the chlorinated cresols, 4-chloro and 6-chloro-o-cresol, have reported to be 75 ug/l and 3 ug/l, respectively (Hoak, 1975).

Several studies have reported the threshold concentrations of chlorinated phenols in water that impart unfavorable flavors in the edible portions of aquatic organisms (Schulze, 1961; Teal, 1959; Shumway, 1966). These threshold values in certain cases are lower than the odor threshold levels in water.

Virtually no data are available on the bioconcentration or bioaccumulation of the lower chlorophenols and limited data are available regarding pentachlorophenol bioconcentration. Studies using 14C-labled 2,4-dichlorophenol (DCP) demonstrated that oats and soybean seedlings concentrated DCP from dilute solutions (0.2 mg/l) by factors of 9.2 and 0.65-fold, respectively (Isensee and Jones, 1971). Bioconcentration data on pentachlorophenol may be found in the pentachlorophenol criterion document.

Chlorophenols, their sodium salts, and certain chlorocresols have been shown to be toxic to aquatic life, mammals, and man. In aquatic organisms it appears that the acute toxicity increases directly with the degree of chlorination. In addition, the production of odors in water and the tainting of fish flesh by the lower chlorophenols and chlorocresols has been reported to occur at extremely low concentrations. These findings, in conjunction with the potential pollution of chlorinated phenols from waste sources, inadvertent chlorination of phenols during disinfection, waste treatment degradation of herbicides and pesticides, and direct industrial and agricultural applications lead to the conclusion that chlorinated phenols represent a potential hazard to aquatic and terrestrial life.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

A review of the available literature on the effects of chlorinated phenols on aquatic life is complicated by the variety of common and scientific names used for these compounds. A consistent set of names has been used herein and footnotes are used to identify other names that were used in referenced publications.

The toxicity of chlorinated phenols to aquatic life varies widely as a function of the nature and degree of ring substitution with chlorine. In general, the toxicity increases with increasing substitution, and in most cases, aquatic plants appear to be less sensitive to these chemicals than aquatic animals.

Because the toxicity of chlorinated phenols to various aquatic life forms is structure-dependent (Tables 1, 2, and 3), giving rise to wide variability, it would be inappropriate to derive a criterion for these chemicals as a group. Instead, these criteria will be derived on the basis of individual chemicals.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The criteria for chlorinated phenols will be derived from the fact that these compounds have been shown to impair the flavor of the edible portions of fish at concentrations lower than those at which they are toxic to aquatic organisms.

Acute Toxicity

The adjusted 96-hour LC50 values for fathead minnows ranged from 21 µg/l for 4-chloro-3-methylphenol (U.S. EPA, 1972) to 9,040 µg/l for 2,4,6-trichlorophenol (Phipps, et al. manuscript).

Daphnia magna was less sensitive than the bluegill for five of the seven chlorinated phenols for which a comparison could be made (Tables 1 and 2).

The 96-hour LC50 values for chlorinated phenols and the bluegill (U.S. EPA, 1978) are directly related to the degree of chlorination. These values decrease from 6,590 µg/l for 2-chlorophenol and 3,830 µg/l for 4-chlorophenol to 60 and 77 µg/l for pentachlorophenol (Bentley, et al. 1975; see pentachlorophenol criterion document). These data and those for intermediate chlorinated phenols can be correlated with the octanol-water partition coefficient with a correlation coefficient of 0.95. Data for other aquatic organisms do not correlate as well.

All but one of the acute tests were run under static conditions and all but three without measured concentrations. In five of the eight cases for which data were available, the Final Invertebrate Acute Values were lower than the Final Fish Acute Values, and thus become the Final Acute Values. These values, with the companion Final Fish Acute Values in parentheses, are: 180 (540) µg/l for 4-chlorophenol, 12 (330) µg/l for 4-chloro-2methylphenol, 17 (230) µg/l for 2,4-dichloro-6-methylphenol, 12 (20) µg/l for

2,3,4,6-tetrachlorophenol, and 23 (24) µg/l for 2,3,5,6-tetrachlorophenol. For two compounds, the Final Fish Acute Values become the Final Acute Values. These values, and the companion Final Invertebrate Acute Values in parentheses are: 150 (240) µg/l for 2,4,6-trichlorophenol and 63 (110) µg/l for 2,4,5-trichlorophenol. Finally, for 4-chloro-3-methylphenol, no Final Invertebrate Acute Value was available, so the Final Fish Acute Value becomes the Final Acute Value, 5.4 µg/l.

Chronic Toxicity

There are no data on the chronic toxicity of chlorinated phenols other than those in the criterion documents for 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol.

Plant Effects

The data in Table 3 indicate that aquatic plants are generally less sensitive to chlorinated phenols than fish or invertebrate species. The chlorosis LC50 values for a series of ten chlorinated phenols (Blackman, et al. 1955) with *Lemna minor* ranged from 598,594 µg/l for 2-chloro-6-methylphenol and 282,832 µg/l for 4-chlorophenol to 603 µg/l for 2,3,4,6-tetrachlorophenol. Once again, the toxicity is related to increasing chlorination but not as clearly as noted for the bluegill. As with fish and aquatic invertebrate species, the derivation of a single Final Plant Value is deemed inappropriate due to the wide variability in toxicity for this group of compounds. The Final Plant Values ranged from 600 µg/l for 2,3,4,6-tetrachlorophenol to 600,000 µg/l for 2-chloro-6-methylphenol.

Residues

No measured steady-state bioconcentration factors (BCF) are available for these chlorinated phenols. Several BCFs can be estimated using the octanol-water partition coefficients of 263, 6,026, 4,898, 19,952, and 6,606 for 4-chlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, and 4-chloro-3-methylphenol, respectively. These coefficients are used to derive estimated BCFs of 41, 440, 380, 1,100, and 470 for 4-chlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, 2,3,4,6-tetrachlorophenol, and 4-chloro-3-methylphenol, respectively, for aquatic organisms that contain about 8 percent lipids. If it is known that the diet of the wildlife of concern contains a significantly different lipid content, appropriate adjustments in the estimated BCFs should be made. Partition coefficients for other chlorinated phenols in this document cannot be estimated.

Miscellaneous

As stated in the introduction, chlorinated phenols have been shown to impair the flavor of fish flesh at concentrations much lower than those at which it has a toxic effect (Shumway and Palensky, 1973). In this study, rainbow trout were exposed for 48 hours to a range of concentrations of five different chlorinated phenols, and a panel of fifteen judges scored the flavor of the cooked and coded fish samples on an increasing impairment scale of 0 to 6. The results were then plotted against exposure concentrations and graphically interpreted to arrive at an estimate of the highest concentration which would not impair the flavor of the flesh. The resulting estimates for five different compounds ranged from 23 µg/l for 2,5-dichlorophenol to 84 µg/l for 2,3-dichlorophenol (Table 4).

CRITERION FORMULATION

Freshwater-Aqautic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

4-chlorophenol

Final Fish Acute Value = 540 µg/l

Final Invertebrate Acute Value = 180 µg/l

Final Acute Value = 180 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 4,800 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 45 µg/l for tainting

0.44 x Final Acute Value = 79 µg/l

2,4,6-trichlorophenol

Final Fish Acute Value = 150 µg/l

Final Invertebrate Acute Value = 240 µg/l

Final Acute Value = 150 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 5,900 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 52 µg/l for tainting

0.44 x Final Acute Value = 66 µg/l

4-chloro-3-methylphenol

Final Fish Acute Value = 5.4 µg/l

Final Invertebrate Acute Value = not available

Final Acute Value = 5.4 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 95,000 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 95,000 μg/l

0.44 x Final Acute Value = 2.4 μg/l

4-chloro-2-methylphenol

Final Fish Acute Value = 330 μg/l

Final Invertebrate Acute Value = 12 μg/l

Final Acute Value = 12 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 93,000 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 93,000 μg/l

0.44 x Final Acute Value = 5.3 μg/l

2,4-dichloro-6-methylphenol

Final Fish Acute Value = 230 μg/l

Final Invertebrate Acute Value = 17 μg/l

Final Acute Value = 17 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = 7.5 μg/l

2,4,5-trichlorophenol

Final Fish Acute Value = 63 µg/l

Final Invertebrate Acute Value = 110 µg/l

Final Acute Value = 63 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 1,200 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 1,200 µg/l

0.44 x Final Acute Value = 28 µg/l

2,3,4,6-tetrachlorophenol

Final Fish Acute Value = 20 µg/l

Final Invertebrate Acute Value = 12 µg/l

Final Acute Value = 12 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 600 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 600 µg/l

0.44 x Final Acute Value = 5.3 µg/l

2,3,5,6-tetrachlorophenol

Final Fish Acute Value = 24 µg/l

Final Invertebrate Acute Value = 23 µg/l

Final Acute Value = 23 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 2,700 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 2,700 μg/l

0.44 x Final Acute Value = 10 μg/l

Flavor impairment studies with rainbow trout exposed to various chlorinated phenols showed that tainting occurred from 23 μg/l to 84 μg/l; and thus tainting will become the basis for criteria. Criteria can be calculated only for 4-chlorophenol and 2,4,6-trichlorophenol since these are the only two chlorinated phenols for which both acute toxicity data and tainting data exist. Tainting was not caused by 4-chlorophenol and 2,4,6-trichlorophenol at 45 μg/l and 52 μg/l, respectively, which are the 24-hour average concentrations. The maximum concentrations of 4-chlorophenol and 2,4,6-trichlorophenol are the Final Acute Values of 180 and 150 μg/l, respectively.

No freshwater criteria can be derived for other chlorinated phenols using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available. There are insufficient data to estimate a criterion using other procedures.

CRITERION: For 2,4,6-trichlorophenol the criterion to protect freshwater aquatic life as derived using the Guidelines is 52 μg/l as a 24-hour average and the concentration should not exceed 150 μg/l at any time.

Table 1. Freshwater fish acute values for chlorinated phenols

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Fathead minnow, *Pimephales promelas*	S	M	2,4,6-trichlorophenol	96	600	426	U.S. EPA, 1972
Fathead minnow (juvenile), *Pimephales promelas*	FT	M	2,4,6-trichlorophenol	96	9,040	9,040	Phipps, et al. Manuscript
Fathead minnow, *Pimephales promelas*	S	M	4-chloro-3-methyl phenol	96	30	21	U.S. EPA, 1972
Bluegill, *Lepomis macrochirus*	S	U	4-chlorophenol	96	3,830	2,094	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S	U	2,4,5-trichlorophenol	96	450	246	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S	U	2,4,6-trichlorophenol	96	320	175	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S	U	2,3,4,6-tetrachlorophenol	96	140	77	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S	U	2,3,5,6-tetrachlorophenol	96	170	93	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S	U	4-chloro-2-methyl-phenol***	96	2,330	1,274	U.S. EPA, 1978
Bluegill, *Lepomis macrochirus*	S	U	2,4-dichloro-6-methyl phenol	96	1,640	897	U.S. EPA, 1978

* S = static, FT = flow-through

** U = unmeasured, M = measured

***Data were reported for 4-chloro-6-methylphenol

Geometric mean of adjusted values: 4-chlorophenol = 2,094 µg/l $\frac{2,094}{3.9}$ = 540 µg/l

2,4,6-trichlorophenol = 586 µg/l $\frac{586}{3.9}$ = 150 µg/l

4-chloro-3-methylphenol = 21 µg/l $\frac{21}{3.9}$ = 5.4 µg/l

4-chloro-2-methylphenol = 1,274 µg/l $\frac{1,274}{3.9}$ = 330 µg/l

Table 1. (Continued)

Organism	Bioassay Method	Test Conc.	Chemical Description	Time (hrs)	LC50 (µg/l)	LC50 (µg/l)	Reference
			2,4-dichloro-6-methylphenyl = 897 µg/l			$\frac{897}{3.9}$ = 230 µg/l	
			2,4,5-trichlorophenol = 246 µg/l			$\frac{246}{3.9}$ = 63 µg/l	
			2,3,4,6-tetrachlorophenol = 77 µg/l			$\frac{77}{3.9}$ = 20 µg/l	
			2,3,5,6-tetrachlorophenol = 93 µg/l			$\frac{93}{3.9}$ = 24 µg/l	

Table 2. Freshwater invertebrate acute values for chlorinated phenols

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC_{50} (µg/l)	Adjusted LC_{50} (µg/l)	Reference
Cladoceran, *Daphnia magna*	S	U	4-chlorophenol	48	4,820	4,082	Kopperman, et al. 1974
Cladoceran, *Daphnia magna*	S	U	4-chlorophenol	48	4,060	3,439	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S	U	2,4,5-trichlorophenol	48	2,660	2,253	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S	U	2,4,6-trichlorophenol	48	6,040	5,116	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S	U	2,3,5,6-tetrachlorophenol	48	570	483	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S	U	2,3,4,6-tetrachlorophenol	48	290	246	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S	U	4-chloro-2-methyl-phenol***	48	290	246	U.S. EPA, 1978
Cladoceran, *Daphnia magna*	S	U	2,4-dichloro-6-methyl phenol	48	430	364	U.S. EPA, 1978

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* S = static

** U = unmeasured

*** Data were reported for 4-chloro-6-methylphenol

Geometric mean of adjusted values:

4-chlorophenol = 3,747 µg/l $\frac{3,747}{21} = 180$ µg/l

2,4,6-trichlorophenol = 5,116 µg/l $\frac{5,116}{21} = 240$ µg/l

2,4,5-trichlorophenol = 2,253 µg/l $\frac{2,253}{21} = 110$ µg/l

2,3,5,6-tetrachlorophenol = 483 µg/l $\frac{483}{21} = 23$ µg/l

4-chloro-2-methylphenol = 246 µg/l $\frac{246}{21} = 12$ µg/l

2,4-dichloro-6-methylphenyl = 364 µg/l $\frac{364}{21} = 17$ µg/l

2,3,4,6-tetrachlorophenol = 246 µg/l $\frac{246}{21} = 12$ µg/l

Table 3. Freshwater plant effects for chlorinated phenols

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Chlorella pyrenoidosa*	Complete destruction of chlorophyll	500,000 mono-chloro-phenols	Huang & Gloyna, 1968
Alga, *Chlorella pyrenoidosa*	Complete destruction of chlorophyll	10,000 2,4,5- and 2,4,6-trichloro-phenols	Huang & Gloyna, 1968
Alga, *Selenastrum capricornutum*	50% reduction in cell production in 96 hrs	4,790 4-chlorophenol	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	50% reduction in chlorophyll *a* in 96 hrs	1,220 2,4,5-trichlorophenol	U.S. EPA, 1978
Alga, *Selenastrum capricornutum*	50% reduction in cell production in 96 hrs	2,660 2,3,5,6-tetrachlorophenol	U.S. EPA, 1978
Duckweed, *Lemna minor*	Chlorosis (LC50)	282,832 4-chlorophenol	Blackman, et al. 1955
Duckweed, *Lemna minor*	Chlorosis (LC50)	1,659 2,4,5-trichlorophenol	Blackman, et al. 1955
Duckweed, *Lemna minor*	Chlorosis (LC50)	5,923 2,4,6-trichlorophenol	Blackman, et al. 1955
Duckweed, *Lemna minor*	Chlorosis (LC50)	603 2,3,4,6-tetrachlorophenol	Blackman, et al. 1955
Duckweed, *Lemna minor*	Chlorosis (LC50)	92,638 4-chloro-2-methylphenol*	Blackman, et al. 1955
Duckweed, *Lemna minor*	Chlorosis (LC50)	598,584 2-chloro-6-methylphenol*	Blackman, et al. 1955
Duckweed, *Lemna minor*	Chlorosis (LC50)	95,488 4-chloro-3-methylphenol*	Blackman, et al. 1955

Table 3. (Continued)

Organism	Effect	Concentration (ug/l)	Reference
Duckweed, Lemna minor	Chlorosis (LC50)	65,479 2,6-dichloro-4-methylphenol*	Blackman, et al. 1955
Duckweed, Lemna minor	Chlorosis (LC50)	6,131 2,4,6-trichloro-3-methylphenol*	Blackman, et al. 1955
Duckweed, Lemna minor	Chlorosis (LC50)	1,107 2,4,5,6-tetrachloro-3-methylphenol*	Blackman, et al. 1955

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*Data were reported for __ methyl __ chlorophenol for these compounds.

Final Plant Values: 4-chlorophenol = 4,800 μg/l

2,4,5-trichlorophenol = 1,200 μg/l

2,4,6-trichlorophenol = 5,900 μg/l

2,3,4,6-tetrachlorophenol = 600 μg/l

2,3,5,6-tetrachlorophenol = 2,700 μg/l

2-methyl-4-chlorophenol = 93,000 μg/l

2-methyl-6-chlorophenol = 600,000 μg/l

3-methyl-4-chlorophenol = 95,000 μg/l

4-methyl-2,6-dichlorophenol = 65,000 μg/l

3-methyl-2,4,6-trichlorophenol = 6,100 μg/l

3-methyl-2,4,5,6-tetrachlorophenol = 1,100 μg/l

Table 4. Other freshwater data for chlorinated phenols

Organism	Test Duration	Effect	Result (ug/l)	Reference
Lymnaeid snails, *Pseudosuccinea columella* and *Fossaria cubensis*	24 hrs	100% mortality	10,000 2,4,5-trichlorophenol	Batte & Swanson, 1952
Lymnaeid snails, *Pseudosuccinea columella* and *Fossaria cubensis*	24 hrs	100% mortality	2,500 sodium 2,4,5-trichlorophenate (85%)	Batte & Swanson, 1952
Lymnaeid snails, *Pseudosuccinea columella* and *Fossaria cubensis*	24 hrs	100% mortality	5,000 2,4,6-trichlorophenol	Batte & Swanson, 1952
Rainbow trout, *Salmo gairdneri*	48 hrs	Lowest concentration which killed 50% or more of the test fish	10,000 3-chlorophenol	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	48 hrs	ETC*	45 4-chlorophenol	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	48 hrs	ETC*	84 2,3-dichlorophenol	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	48 hrs	ETC*	23 2,5-dichlorophenol	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	48 hrs	ETC*	35 2,6-dichlorophenol	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	48 hrs	Lowest concentration which killed 50% or more of the test fish	1,000 2,4,5-trichlorophenol	Shumway & Palensky, 1973
Rainbow trout, *Salmo gairdneri*	48 hrs	ETC*	52 2,4,6-trichlorophenol	Shumway & Palensky, 1973
Goldfish, *Carassius auratus*	8 hrs	62% mortality	20,600 3-chlorophenol	Gersdorff & Smith, 1940

Table 4. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Goldfish, *Carassius auratus*	8 hrs	54% mortality	6,300 4-chlorophenol	Gersdorff & Smith, 1940

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* ETC = the highest estimated concentration of material that will not impair the flavor of the flesh of exposed fish.

SALTWATER ORGANISMS

Introduction

Phenol, and three of the chlorinated phenols, 2-chlorophenol, 2,4-dichlorophenol, and pentachlorophenol are treated in separate water quality criteria documents. The acute toxicity of chlorophenols varies widely, depending on the chlorophenol tested and, therefore, water quality criteria should be derived for individual chlorophenols.

Acute Toxicity

Toxicity tests with the sheepshead minnow have been conducted with three chlorophenols (Table 5). The 96-hour LC50 values, adjusted for static exposures and unmeasured concentrations, range from 908 µg/l for 2,4,5-tetrachlorophenol to 2,924 µg/l for 4-chlorophenol (U.S. EPA, 1978). The Final Fish Acute Values derived from these data using a species sensitivity factor of 3.7 are 790, 250, and 280 µg/l for 4-, 2,4,5-tri-, and 2,3,5,6-tetrachlorophenol, respectively.

Acute toxicity tests with invertebrate species consist of three 96-hour static tests with the mysid shrimp, *Mysidopsis bahia*, and three chlorophenols (Table 6). Using adjusted LC50 values and a species sensitivity factor of 49, the Final Invertebrate Acute Values from these data are 510, 66, and 380 µg/l for 4-, 2,4,5-tri-, and 2,3,5,6-tetrachlorophenol. Final Acute Values are based on Fish or Invertebrate Acute Values, depending on the chlorophenol tested.

Comparable data (U.S. EPA, 1978) are available for effects of other chlorinated phenols on fishes and invertebrate species (see Criterion Documents for 2-chlorophenol, 2,4-dichlorophenol, and

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pentachlorophenol for details). Adjusted LC50 values for fish range from greater than 20,000 µg/l for 2-chlorophenol to 21 µg/l for pentachlorophenol. Adjusted LC50 values for invertebrate species range from 25,155 µg/l for 4-chlorophenol to 34 µg/l for pentachlorophenol. Toxicity of chlorophenols, except 2,3,5,6-tetrachlorophenol and mysid shrimp, appear to increase with increasing degree of chlorination.

Chronic Toxicity

The only chronic data available are those of an embryo-larval test with the sheepshead minnow and 2,4-dichloro-6-methylphenol (Table 7). The lowest concentration tested, 360 µg/l, affected them in a 28-day exposure. Since no acute toxicity test was conducted with this chlorophenol,the value of this chronic test in formulating a water quality criterion is limited.

Plant Effects

Toxicity tests with chlorophenols and the alga, *Skeletonema costatum*, also revealed differences in toxicity, depending upon the compound tested (Table 8). Reductions in chlorophyll *a* and cell numbers showed that 2,3,5,6-tetrachlorophenol was the most toxic and 4-chlorophenol the least toxic. The Final Plant Values for the tested chlorophenols ranged from 440 µg/l for 2,3,5,6-tetrachlorophenol to 3,270 µg/l for 4-chlorophenol.

Comparable test procedures (U.S. EPA, 1978) were used for other chlorophenols and, as with sheepshead minnows and mysid shrimp, toxicity generally increased with increased degree of chlorination.

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CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures.

4-chlorophenol

Final Fish Acute Value = 790 μg/l

Final Invertebrate Acute Value = 510 μg/l

Final Acute Value = 510 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 3,300 μg/l

Residue Limited Toxicant Concentration not available

Final Chronic Value = 3,300 μg/l

0.44 x Final Acute Value = 220 μg/l

2,4,5-trichlorophenol

Final Fish Acute Value = 250 μg/l

Final Invertebrate Value = 66 μg/l

Final Acute Value = 66 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 390 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 890 μg/l

0.44 x Final Acute Value = 29 μg/l

2,3,5,6-tetrachlorophenol

Final Fish Acute Value = 280 μg/l

Final Invertebrate Acute Value = 380 μg/l

Final Acute Value = 280 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 440 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 440 μg/l

0.44 x Final Acute Value = 120 μg/l

2,4-dichloro-6-methylphenol

Final Fish Acute Value = not available

Final Invertebrate Acute Value = not available

Final Acute Value = not available

Final Fish Chronic Value = less than 27 μg/l

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = less than 27 μg/l

0.44 x Final Acute Value = not available

Flavor impairment studies with aquatic organisms indicate that flavor impairment may be an especially important factor in determining water quality criteria for chlorophenols. Unfortunately, data necessary to establish a saltwater criterion based on tainting are unavailable.

For saltwater aquatic life, no criterion for any chlorinated phenol can be derived using the Guidelines, and there are insufficient data to establish a criterion using other procedures.

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Table 5. Marine fish acute values for chlorinated phenols (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Sheepshead minnow, *Cyprinodon variegatus*	S	U	4-chlorophenol	96	5,350	2,924
Sheepshead minnow, *Cyprinodon variegatus*	S	U	2,4,5-trichlorophenol	96	1,660	908
Sheepshead minnow, *Cyprinodon variegatus*	S	U	2,3,5,6-tetrachlorophenol	96	1,890	1,033

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* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-chlorophenol = 2,924 µg/l $\frac{2,924}{3.7} = 790$ µg/l

2,4,5-trichlorophenol = 908 µg/l $\frac{908}{3.7} = 250$ µg/l

2,3,5,6-tetrachlorophenol = 1,033 µg/l $\frac{1,033}{3.7} = 280$ µg/l

Table 6. Marine invertebrate acute values for chlorinated phenols (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Chemical Description	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Mysid shrimp, *Mysidopsis bahia*	S	U	4-chlorophenol	96	29,700	25,155
Mysid shrimp, *Mysidopsis bahia*	S	U	2,4,5-trichlorophenol	96	3,830	3,244
Mysid shrimp, *Mysidopsis bahia*	S	U	2,3,5,6-tetrachlorophenol	96	21,900	18,549

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* S = static

** U = unmeasured

Geometric mean of adjusted values: 4-chlorophenol = 25,155 µg/l $\frac{25,155}{49}$ = 510 µg/l
2,4,5-trichlorophenol = 3,244 µg/l $\frac{3,244}{49}$ = 66 µg/l
2,3,5,6-tetrachlorophenol = 18,549 µg/l $\frac{18,549}{49}$ = 380 µg/l

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Table 7. Marine fish chronic values for chlorinated phenols (U.S. EPA, 1978)

Organism	Test*	Limits** (µg/l)	Chronic** Value (µg/l)
Sheepshead minnow, *Cyprinodon variegatus*	E-L	<360	<180

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* E-L = embryo-larval

** Data for 2,4-dichloro-6-methylphenol

Geometric mean of chronic values = <180 µg/l $\frac{<180}{6.7} = <27$ µg/l

Lowest chronic value = <180 µg/l

Table 8. Marine plant effects for chlorinated phenols (U.S. EPA, 1978)

Organism	Effect	Concentration (µg/l)
		4-chlorophenol
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	3,270
Alga, *Skeletonema costatum*	EC50 96-hr cell count	3,560
		2,4,5-trichlorophenol
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	890
Alga, *Skeletonema costatum*	EC50 96-hr cell count	960
		2,3,5,6-tetrachlorophenol
Alga, *Skeletonema costatum*	EC50 96-hr chlorophyll *a*	440
Alga, *Skeletonema costatum*	EC50 96-hr cell count	500

Final plant value: 4-chlorophenol = 3,270 µg/l

2,4,5-trichlorophenol = 890 µg/l

2,3,5,6-tetrachlorophenol = 440 µg/l

CHLORINATED PHENOLS

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3-CHLOROPHENOL AND 4-CHLOROPHENOL

Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

Monochlorophenol has three isomeric forms, each distinguished by the position of the chlorine atom relative to the hydroxy-group on carbon one of the six-carbon ring. The three isomers are 2-chlorophenol or o-chlorophenol; 3-chlorophenol or m-chlorophenol; and 4-chlorophenol or p-chlorophenol. This document will discuss only 3- and 4-chlorophenol since 2-chlorophenol was addressed in a separate criterion document.

Monochlorophenols have been used as antiseptics since 1893 (Von Oettingen, 1949). They occur as intermediates in the formation of other chlorophenol-containing products and as metabolic breakdown products of other chlorophenols or chlorobenzene. They may also be formed by the chlorination of water containing natural phenol or phenolic wastes.

The chemical properties of 3- and 4-chlorophenol are listed in Table 1. One important property is the ability of relatively low concentrations of chlorophenols to produce a medicinal odor and taste in water. This low organoleptic threshold may call attention to a state of contamination and aid in protecting humans from unacceptable levels of exposure.

Phenols are known to occur naturally in the environment (Hoak, 1957). For example, some aquatic plants release sufficient phenol to establish water levels of 300-960 µg/l. Phenols are found in raw domestic sewage at levels of 70-

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TABLE 1

Properties of Mono-Chlorophenols

3-Chlorophenol

Alternate name	m-chlorophenol
Molecular weight	128.56
Specific gravity	1.268
Form at room temperature	needles
Melting point	32°C
Boiling point	214°C
Solubility	
water	slightly soluble
alcohol	soluble
ether	soluble
benzene	very soluble
Vapor pressure	1 mm Hg at 44.2°C
CAS number	000108430
Odor threshold in water-30°C	0.2 µg/l (Hoak, 1957)

4-Chlorophenol

Alternate name	p-chlorophenol
Molecular weight	128.56
Specific gravity	1.306
Form at room temperature	needles
Melting point	41°C
Boiling point	217°C
Solubility	
water	very slightly soluble
alcohol	very soluble
ether	very soluble
benzene	very soluble
Vapor pressure	1 mm Hg at 49.8°C
CAS number	000106489
Odor threshold in water-30°C	0.03 µg/l (Hoak, 1957)

100 ug/l. Complex phenols are at least partially released by bacterial action in sewage treatment trickling filters. The decomposition of surface vegetation such as oak leaves also releases phenol.

The association of bad taste or odor in tap water with chlorophenols has been of interest for a number of years. Hoak (1957) reviewed aspects of this problem. Some chlorophenols have odor thresholds in the ppb concentration range. The addition of 0.2-0.7 ppm chlorine to water containing 100 ppb phenol results in the development of a chlorophenol taste. Increasing the level of chlorine or increasing the reaction time reduces the taste. Odor thresholds for chlorophenols in water are shown in Table 2. The thresholds for mono- and dichlorophenol are very low.

The threshold concentrations of the monochlorophenols in water that impart an offensive flavor to the edible portion of the flesh of aquatic organisms have been reported. A summary of the data is presented in Table 2a.

Burttschell, et al. (1959) proposed a mechanism for the chlorination of phenol in water. According to their scheme 2- and 4-chlorophenol are formed early. These molecules are further chlorinated to 2,6- or 2,4-dichlorophenol. The final product is 2,4,6-trichlorophenol. After 18 hours of reaction, the chlorophenol products in Burttschell's study consisted of less than 5 percent each 2- and 4-chlorophenol, 25 percent 2,6-dichlorophenol, 20 percent 2,4-dichlorophenol and 40 to 50 percent 2,4,6-trichlorophenol.

TABLE 2

Comparison of Odor Thresholds for Chlorophenols in Water

	Threshold-ppb (μg/l)	Reference
2-chlorophenol	0.33 ppb - 30°C	1
2-chlorophenol	2 ppb - 25°C	2
2-chlorophenol	6 ppb - NS	3
3-chlorophenol	200 ppb - 30°C	1
4-chlorophenol	33 ppb - 30°C	1
4-chlorophenol	250 ppb - 25°C	2
4-chlorophenol	900 - 1350 ppb	3
2,4-dichlorophenol	0.65 ppb - 30°C	1
2,4-dichlorophenol	2 ppb - 25°C	2
2,5-dichlorophenol	3.3 ppb - 30°C	1
2,6-dichlorophenol	3 ppb - 25°C	2
2,4,5-trichlorophenol	11 ppb - 25°C	1
2,4,6-trichlorophenol	100 ppb - 30°C	1
2,4,6-trichlorophenol	1000 ppb - 25°C	2
2,3,4,6-tetrachlorophenol	915 ppb - 30°C	1

1 - Hoak, 1957
2 - Burttschell, et al. 1959
3 - Campbell, et al. 1958
NS - temperature not specified

TABLE 2a

SUMMARY OF THRESHOLD CONCENTRATIONS OF CHLORINATED PHENOLS IN WATER THAT CAUSE TAINTING OF THE FLESH OF AQUATIC ORGANISMS

Compound	Threshold(ug/l)	Reference a/
2-chlorophenol	15.0	5
	15.0	6
3-chlorophenol	60.0	5
4-chlorophenol	60.0	5
	50.0	6
2,4-dichlorophenol	5.0	6
	10.0	7

a) 5 - Schulze, E. 1961. The effect of phenol-containing waste on the taste of fish. Int. Revue Ges. Hydrobiol. 46, No. 1, p. 81

6 - Teal, J. L. 1959. The control of waste through fish taste. Presented to American Chemical Society, National Meeting.

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Ingestion from Water

Burttschell, et al. (1959) demonstrated that the chlorination of water containing phenol could result in the formation of chlorophenols including mono-, di-, and trichlorophenol isomers. Piet and De Grunt (1975) found monochlorophenols in surface waters in the Netherlands at concentrations of 2 to 20 µg/l (ppb). A level of 20 µg/l in water, consumed at a rate of 2 l/day by a 70 kg individual, would result in an exposure of 0.57 µg/kg.

Another source of chlorophenols in water is the chlorination of sewage. Jolley, et al. (1975) analyzed chlorinated sewage treatment plant effluents and found 0.5 µg/l of 3-chlorophenol and 0.7 µg/l of 4-chlorophenol. Ingols, et al. (1966) studied the biological degradation of chlorophenols in activated sludge. Both 3- and 4-chlorophenol at levels of 100 mg/l were completely degraded in three days with 100 percent ring degradation.

Alexander and Aleem (1961) studied the microbial decomposition of chlorophenols in soil suspensions. 3-Chlorophenol did not disappear completely in 47 or 72 days when tested with two soil types. 4-Chlorophenol disappeared in three or nine days in the two soil types.

The ingestion of chlorobenzene may also give rise to an internal metabolic exposure to chlorophenol. The mammalian metabolism of chlorobenzene yields 2-, 3-, and 4-chlorophenol as the major products (Lindsay-Smith, et al. 1972).

Ingestion from Foods

No data were found demonstrating the presence of monochlorophenols in food.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for 4-chlorophenol, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about eight percent lipids from the octanol-water partition coefficient (P). An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for the edible portion of all aquatic organisms consumed by Americans can be calculated.

Compound	P	BCF	Weighted BCF
4-chlorophenol	260	40	12

Inhalation

No data were found regarding the presence of monochlorophenols in air.

Dermal

Roberts, et al. (1977) used human autopsy skin epidermal membranes in an *in vitro* test system to determine the permeability of the human skin to various chemicals. 4-Chlorophenol was shown to permeate the skin, and to produce damage at a threshold concentration of 0.75 percent (w/v).

PHARMACOKINETICS

No systematic studies of the pharmacokinetics of 3- or 4-chlorophenol in man or laboratory animals were found. However, Karpow (1893) reported that 87 percent of 4-chlorophenol was excreted in urine of dogs as sulfuric and glucuronic conjugates.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

The acute oral, subcutaneous, dermal, intraperitoneal, and inhalation LD50's for 3- and 4-chlorophenol are shown in Table 3. Because 3-chlorophenol is a liquid at room temperature, some of the early workers reported LD50's as ml/kg. The oral LD50 for each isomer is on the order of 500 to 600 mg/kg. The dermal LD50 for 4-chlorophenol is 1,500 mg/kg, indicating dermal absorption. Interestingly, both 3- and 4- chlorophenol are less toxic when given subcutaneously than when taken orally. This may reflect a slower absorption from the injection site and a rapid metabolism of the absorbed compounds.

4-Chlorophenol applied dermally causes skin irritation and necrosis in rabbits, rats, and guinea pigs. Dermal exposure can result in convulsive seizures (Gurova, 1964).

Cats survived four doses of 40 mg/kg of 4-chlorophenol administered intraperitoneally at three-hour intervals (Miller, et al. 1973).

The monochlorophenols act on the nervous system to produce tremors and convulsions, an effect reported several times in the literature. The monochlorophenols with a pKa

TABLE 3

Acute Toxicity of Monochlorophenols

CHEMICAL	SOLVENT	SPECIES	TOXIC RESPONSE	REFERENCE
3-chlorophenol	olive oil	rat	oral LD50 = 0.56 ml/kg	Deichmann and Mergard, 1948
	olive oil	rat	subQ LD50 = 1.39 ml/kg	Deichmann and Mergard, 1948
	olive oil	rat	i.p. LD50 = 335 mg/kg	Farquharson, et al. 1958
4-chlorophenol	not stated	rat	oral LD50 = 500 mg/kg	Gurova, 1964
	olive oil	rat	oral LD50 = 660 mg/kg	Deichmann and Mergard, 1948
	not stated	mouse	oral LD50 = 860 mg/kg	Schrotter, et al. 1977
	olive oil	rat	subQ LD50 = 1030 mg/kg	Deichmann and Mergard, 1948
	not stated	rat	dermal LD50 = 1500 mg/kg	Gurova, 1964
	olive oil	rat	i.p. LD50 = 250 mg/kg	Farquharson, et al. 1958
		mouse	inhalation LD50 11 mg/m^3	Gurova, 1964

of 8 or greater are convulsants. At body pH (7.0 to 7.4), these chlorophenols are largely undissociated.

Binet (1896) reported that subcutaneous injections of monochlorophenols in rats and guinea pigs caused muscle twitching, spasms, generalized tremors, weakness, staggering, and finally collapse. Kuroda (1926) found that intravenous doses of 100 mg/kg of any of the three monochlorophenol isomers caused convulsions in rabbits.

In acutely toxic doses 3-chlorophenol causes restlessness and increased respiration followed by rapidly developing motor weakness (Deichmann, 1943). Clonic convulsive seizures follow and continue until death. The clinical signs are similar with 4-chlorophenol but the convulsions are more severe.

Farquharson, et al. (1958) also reported that 2-, 3-, or 4-chlorophenol produced convulsive seizures in rats. Body temperature was reduced 2 to 5°C, and rigor mortis did not develop within five minutes of death as with tri-, tetra-, and pentachlorophenol. Death occurred one hour after dosing in rats given the LD50. At higher doses, deaths occurred in five to fifteen minutes. There were no further deaths in rats surviving three hours. Convulsions occurred as soon as one to two minutes following intraperitoneal injection. 4-Chlorophenol and 3-chlorophenol also stimulated oxygen uptake by rat brain homogenate at concentrations between 2.5×10^{-5} and 1×10^{-3}M.

Angel and Rogers (1972) used urethane-anesthetized mice to determine the CD50, i.e., the intraperitoneal dose required to produce convulsions in 50 percent of the test animals. The CD50's were 100.6 mg/kg for 3-chlorophenol and 115.7 mg/kg for 4-chlorophenol. Both of these monochlorophenols have approximately 1.2 times the convulsant potency of phenol. These CD50 values are approximately one-half to one-third of the intraperitoneal LD50.

Hanig, et al. (1976) demonstrated that hexachlorophene elevated the cerebrospinal fluid pressure in the rat and cat; 4-chlorophenol did not.

Gurova (1964) conducted inhalation studies of 4-chlorophenol using mice and rats. The inhalation LD50 for mice was 11 mg/m^3, with the duration of exposure not reported. Single inhalations of 20 mg/m^3 for an unknown duration did not produce acute poisoning in rats. Rats exposed to 13 mg/m^3 for two hours showed increased neuromuscular excitability based on response to peripheral nerve electrical stimulation. These animals also experienced increased oxygen consumption. Mice were more sensitive since 2 mg/m^3 increased their oxygen consumption.

Rats exposed 6 hrs/day for four months to 2 mg/m^3 showed a weight loss during the first 30 days followed by an increased weight gain. These animals also showed an increased myoneural excitability. Body temperature, hemoglobin, RBC, WBC, and sedimentation rate were not altered.

Lesions in inhalation-exposed and inhalation-poisoned animals were described by Gurova (1964). Congestion and focal hemorrhages were observed in brain, lungs, liver, kidney, and myocardium. Lung pathology consisted of thickened alveolar septa, atelectasis, and emphysema. Degenerative changes occurred in brain cortical and glia cells and in liver and myocardium.

Banna and Jabbur (1970) studied the effects of phenols on nerve synaptic transmission in cats. Phenol, like the monochlorophenols, is a convulsant. The mechanism of action apparently involves an increase in the amount of neurotransmitter released at the nerve synapse.

In terms of mechanism of action studies most efforts have been directed toward effects on oxidative phosphorylation and enzymes involved in carbohydrate and intermediary metabolism and ATP.

Parker (1958) studied the effect of chlorophenols on isolated rat liver mitochondria metabolism. 2,4-Dinitrophenol was used as a reference compound because of its known ability to uncouple oxidative phosphorylation. 4-Chlorophenol at $2.8 \times 10^{-4}M$ had 21 percent of the activity of $2 \times 10^{-5}M$ of 2,4-dinitrophenol.

Mitsuda, et al. (1963) studied the effects of various chlorophenols on oxidative phosphorylation in isolated rat liver mitochondria. The test system used a 2.75 ml reaction medium at pH 7.0, containing 0.05 ml of mitochondrial suspension with 0.43 mg N. The ID50 (concentration of chlorophenol required to produce a 50 percent inhibition in the production of ATP) was determined. The I_{50} values for the monochlorophenols were 520 µM, 150 µM, and 180 µM for 2-, 3-, and 4-chlorophenol, respectively. For comparison, the I_{50}'s for pentachlorophenol and 2,4-dinitrophenol are 1 µM and 17 µM, respectively.

Weinbach and Garbus (1965) tested the ability of various substituted phenols to completely uncouple oxidative phosphorylation *in vitro*. 3-Chlorophenol and 4-chlorophenol caused complete uncoupling at 2.5 mM. For comparison, the known uncoupler 2,4-dinitrophenol completely uncoupled the test system at 0.1 mM. There was a positive relationship between mitochondria protein binding and uncoupling properties.

During the past years one research group has developed a novel approach to studying the potential effects of chemicals on the eye. Ismail, et al. (1976) studied the permeation of a number of chemicals, including 2-chlorophenol into the bovine lens capsule and examined the subsequent effects on lens enzymes. Their hypothesis was that environmental chemicals may be responsible for eye diseases or lens opacities. 3,4-Dichlorophenol was found to rapidly permeate the lens capsule. Using a concentration of 10^{-4}M (16 mg/l) of 3,4-dichlorophenol, the activity of various enzymes in the bovine lenses was compared with control lenses. No statistical analysis was reported; the results are presented in Table 4. For comparison the activity of 2-chlorophenol, the only other chlorophenol tested, is presented. The response pattern is complex and difficult to interpret in the absence of statistical analysis.

TABLE 4

Effect[a] of Chlorophenols on Enzyme Activities of Isolated Bovine Lenses. (Ismail, et al. 1976)

Enzyme	2-chlorophenol[b]	3,4-dichlorophenol[b]
Lactic dehydrogenase	94.0	85.5
Malate dehydrogenase	64.4	86.3
Sorbitol dehydrogenase	91.9	107.3
Glucose-6-phosphate dehydrogenase	129.9	70.0
Fructose-diphosphate aldolase	80.4	85.7
Pyruvate kinase	92.9	99.0
Glutamate-oxalacetate-transaminase	92.7	111.9
Flutamate-pyruvate-transaminase	142.9	92.9

[a] The effect is expressed as percent of control.
[b] Each chemical was tested at 10^{-4}M.

Korte, et al. (1976) have used the isolated bovine lens system to study the metabolic effects of various chemicals on this part of the eye. One lens is used as a control and the other as the experimental. 4-Chlorophenol at 10^{-3}M reduced ATP, glucose-6-phosphate, glucose and fructose levels after a 48-hour incubation. 3-Chlorophenol reduced levels of fructose, ATP and ADP, and increased AMP levels. Korte, et al. (1976) did not find changes in the following dehydrogenases: lactate, malate, sorbital, glucose-6-phosphate or in fructose 1,6-diphosphate aldolase or pyruvate kinase.

Harrison and Madonia (1971) pointed out that 4-chlorophenol has been used since the nineteenth century at a concentration of 35 percent in camphor for endodontic therapy in dentistry. They conducted ocular and dermal toxicity tests with one or two percent aqueous solutions of 4-chlorophenol and 35 percent camphorated 4-chlorophenol. The one percent aqueous solution caused slight hyperemia when 0.15

ml was placed on the cornea of white rabbits. A two percent aqueous solution (0.15 ml) produced a more severe response, characterized by moderate to severe hyperemia, mild to moderate edema, cloudy cornea and exudation. The 35 percent camphorated 4-chlorophenol produced a severe response. The changes induced by the one percent and two percent aqueous solutions became evident after five minutes, were most intense after five hours, and subsided by 96 hours post-administration. Harrison and Madonia also injected 0.1 ml of each solution intradermally in rabbits. The one and two percent aqueous parachlorophenol solutions produced mild inflammation after 24 and 72 hours. The 35 percent camphorated 4-chlorophenol caused a severe inflammatory response including necrosis. The authors concluded that one percent aqueous parachlorophenol was a better choice for an antimicrobial intracanal medication.

Gurova (1964) reported the effects of 4-chlorophenol in industrial workers in an aniline dye plant in Russia. Air levels ranged from 0.3 to 21 mg/m^3 depending on the work site and operation. Two accidental acute poisonings were reported with clinical signs consisting of headache, dizziness, respiratory disorder, vomiting, loss of coordination, tremor and, in one case, liver enlargement. Other workers not acutely affected reported experiencing headache, dizziness, weakness, nausea, vomiting and paresthesia (abnormal spontaneous sensation). A health survey was done comparing workers exposed to 4-chlorophenol with unexposed workers in the same plant. The 4-chlorophenol workers had a significantly higher incidence of neurologic disorders. Symptoms reported included neurasthenia (nervous exhaustion), insomnia, irritability, frequent mood changes and rapid fatigability. Peripheral nerve stimulation studies showed increased myoneural excitability in exposed workers. A decreased response to a two-point touch discrimination was apparent, in that the minimum detection distance between the points was increased. Changes in the capillaries of the nail fold of the fingers were said to occur, but were not described. An average permissible air concentration of 3 mg/m^3 was reported for industrial workers.

Synergism and Antagonism

No information was found describing synergistic or antagonistic effects associated with 3- or 4-chlorophenol.

Teratogenicity

No information was found regarding the presence or absence of teratogenic properties of 3- or 4-chlorophenol.

Mutagenicity

No information was found regarding the presence or absence of mutagenic properties of 3- or 4-chlorophenol.

Carcinogenicity

No adequate information was found to determine whether or not 3- or 4-chlorophenol possess carcinogenic properties.

Boutwell and Bosch (1959) conducted a series of experiments on the tumor promoting action of substituted phenols using repeated applications of concentrated solutions to the backs of mice. A 20 percent solution of 3-chlorophenol in benzene increased the number of papillomas, but no carcinomas were found after 15 weeks (Table 5). The tumor initiator

DMBA (9,10-dimethyl-1,2-benzanthracene) was used. Papillomas occurred at the application site.

TABLE 5

Papilloma Promoting Action of 3-Chlorophenol[a].
(Boutwell and Bosch, 1959)

	Group	
	Control	3-chlorophenol (20%)
Number of mice (survivors/original)	15/20	21/33
Average number of papillomas per survivor	0.07	1.38
Percent survivors with papillomas	7	67
Percent survivors with carcinomas	0	0

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[a] Promoter applied twice weekly. Initiator 0.3% DMBA in benzene. Promoter in benzene.

CRITERION FORMULATION

The information of this section is presented in a composite treatment of the chlorophenols at the end of the document.

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2,5-DICHLOROPHENOL, 2,6-DICHLOROPHENOL, 3,4-DICHLOROPHENOL AND 3,5-DICHLOROPHENOL

Mammalian Toxicology and Human Health Effects

SUMMARY

There are several isomers of dichlorophenol. The most common is 2,4-dichlorophenol, which is reviewed in another document in this series. The remaining dichlorophenol isomers apparently have not found use as primary chemicals. The following isomers are discussed in this document: 2,5-, 2,6-, 2,3-, 4,6- and 3,4-dichlorophenol. Physiochemical properties of these compounds are listed in Table 1. The dichlorophenols can be formed either as intermediates in the chlorination of phenol to higher chlorophenols, or as degradation products. A limited amount of work has been reported on dichlorophenols other than the 2,4-isomer.

TABLE 1

Physiochemical Properties[a]

Property	Dichlorophenol Isomer			
	2,5-	2,6-	3,4-	3,5-
Molecular weight	163	163	163	163
Formula	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$	$C_6H_4Cl_2O$
Melting point °C	59	68-9	68	68
Boiling point °C	211	219	253	233
Density	-	-	-	-
Solubility				
water	slightly	-	slightly	slightly
alcohol	very	very	very	very
ether	very	very	very	very
acetone	-	-	-	-
benzene	soluble	soluble	soluble	-
Vapor pressure-mm Hg (pressure, °C)	-	1mm, 59°	-	-
CAS number*	N.L.	N.L.	N.D.	N.L.

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*N.L. not listed in toxic substance list

N.D. listed in toxic substances list, but no CAS registery number given

[a] Source: Handbook of Chemistry and Physics, 59th Edition, R.C. Weast, Editor, CRC Press, 1978.

Phenols are known to occur naturally in the environment (Hoak, 1957). For example, some aquatic plants release sufficient phenol to establish water levels of 300-960 ug/l. Phenols are found in raw domestic sewage at levels of 70-100 ug/l. Complex phenols are at least partially released by bacterial action in sewage treatment trickling filters. The decomposition of surface vegetation such as oak leaves also releases phenol.

The association of bad taste or odor in tap water with chlorophenols has been of interest for a number of years. Hoak (1957) reviewed aspects of this problem. Some chlorophenols have odor thresholds in the ppb concentration range. The addition of 0.2-0.7 ppm chlorine to water containing 100 ppb phenol results in the development of a chlorophenol taste. Increasing the level of chlorine or increasing the reaction time reduces the taste. Odor thresholds for chlorophenols in water are shown in Table 2. The thresholds for mono- and dichlorophenol are very low.

The threshold concentration of 2,4-dichlorophenol in water that imparts an unfavorable odor to the flesh of aquatic organisms is presented in Table 2a. In this instance the reported odor threshold level of this compound in water is lower than the tainting threshold level.

Burttschell, et al. (1959) proposed a mechanism for the chlorination of phenol in water. According to their scheme 2- and 4-chlorophenol are formed early. These molecules are further chlorinated to 2,6- or 2,4-dichlorophenol. The final product is 2,4,6-trichlorophenol. After 18 hours of reaction, the chlorophenol products in Burttschell's study consisted of less than 5 percent each 2- and 4-chlorophenol, 25 percent 2,6-dichlorophenol, 20 percent 2,4-dichlorophenol and 40 to 50 percent 2,4,6-trichlorophenol.

TABLE 2

Comparison of Odor Thresholds for Chlorophenols in Water.

	Threshold-ppb (µg/l.)	Reference[a]
2-chlorophenol	0.33 ppb - 30° 2 ppb - 25° 6 ppb - NS[b]	1 2 3
3-chlorophenol	200 ppb - 30°C	1
4-chlorophenol	33 ppb - 30°C 250 ppb - 25°C 900 - 1350 ppb	1 2 3
2,4-dichlorophenol	0.65 ppb - 30°C 2 ppb - 25°C	1 2
2,5-dichlorophenol	3.3 ppb - 30°C	1
2,6-dichlorophenol	3 ppb - 25°C	2
2,4,5-trichlorophenol	11 ppb - 25°C	1
2,4,6-trichlorophenol	100 ppb - 30°C 1000 ppb - 25°C	1 2
2,3,4,6-tetrachlorophenol	915 ppb - 30°C	1

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a) 1 - Hoak, 1957
2 - Burttschell, et al., 1959
3 - Campbell, et al., 1958

b) NS - temperature not specified

TABLE 2a

SUMMARY OF THRESHOLD CONCENTRATIONS OF CHLORINATED PHENOLS IN WATER THAT CAUSE TAINTING OF THE FLESH OF AQUATIC ORGANISMS

Compound	Threshold(ug/1)	Reference a/
2-chlorophenol	15.0	5
	15.0	6
3-chlorophenol	60.0	5
4-chlorophenol	60.0	5
	50.0	6
2,4-dichlorophenol	5.0	6
	10.0	7

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EXPOSURE

Introduction

There are no quantitative data available to indicate that humans are exposed to the dichlorophenols under discussion. This section will briefly review existing reports regarding potential exposure to dichlorophenols.

Ingestion from Water

Piet and DeGrunt (1975) found unspecified dichlorophenol isomers in Dutch surface waters in concentrations of 0.01-1.5 µg/l. Burttschell, et al. (1959) demonstrated that the chlorination of phenol-laden water could result in the formation of mono-, di-, and trichlorophenol isomers.

Ingols, et al. (1966) studied the biological degradation of chlorophenols in activated sludge. 2,5-Dichlorophenol was more resistent to degradation than 2,4-dichlorophenol. While 2,4-dichlorophenol was 100 percent degraded, including ring degradation, in five days, 2,5-dichlorophenol was only 52 percent ring degraded in four days.

Crosby and Wong (1973) reported that the photodecomposition of the herbicide 2,4,5-T results in the formation of small amounts of 2,5-dichlorophenol.

Alexander and Aleem (1961) determined the microbial decomposition of 2,5-dichlorophenol in a Dunkirk soil suspension. Disappearance was not complete at the end of 72 days.

Ingestion from Foods

No data were available regarding exposure via ingestion of dichlorophenols from foods.

Inhalation

Olie, et al. (1977) reported finding di-, tri- and tetrachlorphenols in flue gas condensates from municipal incinerators. The levels were not quantified.

Dermal

No data were available.

PHARMACOKINETICS

Pharmacokinetic data specific to these dichlorophenol isomers were not available. It is reasonable to assume that dichlorophenol isomers are absorbed through the skin and from the gut, and rapidly eliminated from the body, as are other chlorophenols.

Metabolism

Dichlorobenzenes are metabolized by mammals to dichlorophenols (Kohli, et al. 1976). For example, 1,2-dichlorobenzene gives rise to 3,4-dichlorophenol and smaller amounts of 2,3-dichlorophenol, 3,4- and 4,5-dichlorophenol and 3,4-dichlorophenylmercapturic acid.

Foster and Saha (1978) reported that chicken liver homogenates would metabolize lindane and the alpha and delta but not the beta isomers of 1,2,3,4,5,6, hexachlorocyclohexane. The metabolic products included 2,4,6-trichlorophenol, 2,3-dichlorophenol as well as di- and trichlorobenzenes.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Farquharson, et al. (1958) reported that 2,6-dichlorophenol produced convulsions in rats. The intraperitoneal LD50 was 390 mg/kg. Rats given the LD50 died in one hour; deaths did not occur later in rats surviving three hours. Body temperature was depressed 0.7°C, and rigor mortis did not occur within five minutes of death as it does with higher chlorinated phenols. Oxygen consumption by rat brain homogenate was stimulated at concentrations between 2.5×10^{-5} and 1×10^{-3} M.

Banna and Jabbur (1970) studied the effects of phenols, but not chlorophenols directly, on nerve synaptic transmission in cats. Phenol is a convulsant, as are the lower chlorinated phenols. Experimental results suggest that the mechanism of action involves an increase in the amount of neurotransmitter released at the new synapse.

Hanig, et al. (1976) demonstrated that hexachlorophene, but not 4,6-dichlorophenol, elevated the cerebrospinal fluid pressure in rat and cat.

The mechanism of action studies reported have primarily focused on effects on oxidative phosphorylation. Korte, et al. (1976) studied the effect of 3,4-dichlorophenol on carbohydrate metabolism and enzyme activity in the incubated bovine lens. At a concentration of 10^{-3} M, 3,4-dichlorophenol decreased ATP and ADP levels while increasing AMP levels. There was no effect on glucose or fructose-6-phosphate levels. Activities of malate dehydrogenase, glucose-6-phosphate dehydrogenase and pyruvate kinase were reduced. The dichlorophenol caused swelling of the lens.

Ismail, et al. (1976) studied the permeation of chemicals into the bovine lens capsule and the effects on lens enzymes. Their hypothesis is that environmental chemicals may be responsible for eye diseases or lens opacities. 3,4-Dichlorophenol was found to permeate the lens capsule rapidly. Using a concentration of 10^{-4} M (16 mg/L) of 3,4-dichlorophenol, the activity of various enzymes in the bovine lenses was compared with control lenses. Since no statistical analysis was reported, the results are presented in Table 3. For comparison, data on the activity of 2-chlorophenol, the only other chlorophenol tested, are presented. The response pattern is complex and difficult to interpret in the absence of statistical analysis.

TABLE 3

Effect[a] of Chlorophenols on Enzyme Activities of Isolated Bovine Lenses. (Ismail, et al. 1976)

Enzyme	2-chlorophenol[b]	3,4-dichlorophenol[b]
Lactic dehydrogenase	94.0	85.5
Malate dehydrogenase	64.4	86.3
Sorbitol dehydrogenase	91.9	107.3
Glucose-6-phosphate dehydrogenase	129.9	70.0
Fructose-diphosphate aldolase	80.4	85.7
Pyruvate kinase	92.9	99.0
Glutamate-oxalacetate-transaminase	92.7	111.9
Glutamate-pyruvate-transaminase	142.9	92.9

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[a] The effect is expressed as percent of control.
[b] Each chemical was tested at 10^{-4} M.

Synergism and/or Antagonism

No information was found describing synergistic or antagonistic effects associated with the dichlorophenols.

Teratogenicity

No reports were found relating to the presence or absence of teratogenic properties of the dichlorophenol isomers covered in this document.

Mutagenicity

Rasanen and Hattula (1977) tested chlorophenols for mutagenicity using the Salmonella-mammalian microsome Ames test with both the non-activated and liver homogenate added systems. The following dichlorophenol isomers were tested and reported as non-mutagenic in both test systems: 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dichlorophenol. Mutagenicity in mammalian test systems has not been evaluated.

Carcinogenicity

No reports were found in which the carcinogenic properties of the dichlorophenol isomers covered in this document were determined.

CRITERION FORMULATION

The information of this section is presented in a composite treatment of the chlorophenols at the end of the document.

REFERENCES

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TRICHLOROPHENOLS

Mammalian Toxicology and Human Health Effects

SUMMARY

Trichlorophenols are used as antiseptics and disinfectants, as well as being intermediates in the formation of other chemical products. The most widely recognized of a number of possible isomers is 2, 4, 5-trichlorophenol. Other isomers include: 3, 4, 5-, 2, 4, 6-, 2, 3, 4-, 2, 3, 5-, and 2, 3, 6-trichlorophenol. The physiochemical properties of these isomers are listed in Table 1. The toxic substances list includes only the 2, 4, 6- and 2, 4, 5- isomers.

In the evaluation of the trichlorophenols there is a related contaminant that is the subject of specific but separate consideration by regulatory agencies, including the U.S. Environmental Protection Agency.

A major use of 2, 4, 5- trichlorophenol is as a feedstock in the synthesis of various pesticides, including the herbicides 2, 4, 5- trichlorophenoxyacetic acid (2, 4, 5-T), silvex, erbon and the insecticide ronnel. All of these products involve 2, 4, 5- trichlorophenol in their manufacturing processes and may involve 2, 3, 7, 8- tetrachlorodibenzo-p-dioxin (TCDD). This highly toxic contaminant caused EPA to publish a Rebuttable Presumption Aganist Registration (RPAR) and Continued Registration of Pesticide Products Containing 2, 4, 5-T (Federal Register 43: 17116). The published RPAR indicated that 2, 4, 5- trichlorophenol is

TABLE 1

Physiochemical Properties of Trichlorophenols

Properties	Trichlorophenol Isomers			
	2,3,4	2,3,5	2,3,6	2,4,5
Moleclar Weight	197.45	197.45	197.45	197.45
Formula	C_6H3Cl_3O	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$
Melting point °C	83.5	62	58	68-70
Boiling point °C	sublimes	248.5	--	sublimes
Density	--	--	--	--
Solubility				
water	--	slightly	slightly	slightly
alcohol	soluble	soluble	very	soluble
ether	soluble	soluble	very	--
acetone	--	--	--	--
benzene	soluble	--	very	--
Vapor pressure mm Hg (pressure, °C)	--	--	--	1 mm, 72°
CAS Number*	NL	NL	NL	000095954

Source: Handbook of Chemistry and Physics, 59th Edition, R. C. Weast, Ed., CRC Press, 1978

*NL = not listed in toxic substances list

TABLE 1 (Cont)
Physiochemical Properties of Trichlorophenols
(continued)

Properties	Trichlorophenol Isomers	
	2,4,6	3,4,5
Molecular weight	197.5	197.5
Formula	$C_6H_3Cl_3O$	$C_6H_3Cl_3O$
Melting point °C	69.5	101
Boiling point °C	246	271-7
Density	1.490	--
Solubility		
water	slightly	slightly
alcholol	soluble	--
ether	soluble	soluble
acetone	--	--
benzene	--	--
Vapor pressure		
mm Hg (pressure, °C)	1mm, 76°	--
CAS Number*	000088062	NL

Source: Handbook of Chemistry and Physics, R . C. Weast, Ed., CRC Press, 1978

*NL = not listed in toxic substances list the subject of a separate potential RPAR.

TCDD is a known teratogen (Courtney, 1976) and carcinogen (Van Miller, et al., 1978). Its extreme toxicity is not disputed. The water solubility of TCDD is 0.2 µg/l. TCDD is produced during the formation of 2, 4, 5- trichlorophenol. Most documented cases of adverse health effects have involved industrial accidents where exothermic reactions resulted in explosions and exposure to humans and the environment. Whiteside (1977) reported on a 1949 explosion of a 2, 4, 5-T process that resulted in 228 cases of chloracne. Chloracne is generally recognized as one of the outward and early symptoms of TCDD toxicosis. Others have reported chloracne in employees in 2, 4-D and 2, 4, 5-T plants (Bleiberg, et al., 1964). The 1976 explosion in Seveso, Italy in which 1-5 kg of TCDD were released has received much lay and scientific attention.

A complete assessment of the toxicity of TCDD in trichlorophenol derived chemicals is beyond the scope of this document. The RPAR published in the Federal Register presents the critical studies for evaluation. No tolerance level has been established for TCDD.

EXPOSURE

Introduction

Currently available data regarding general population and occupational exposure to trichlorophenols are limited. Available data will be discussed in this section.

Chlorophenols as a chemical class tend to be rapidly eliminated in the urine. Hence, analyzing urine for trichlorophenol residues is a reasonable approach to estimating exposure, regardless of the source and route of exposure. Dougherty and Piotrowska (1976) used negative chemical ionization mass spectrometry to analyze urine samples for chlorophenols. Evidence was obtained suggesting the presence of trichlorophenol or trichlorophenoxyl herbicides in 9 to 67 percent of the 57 samples analyzed. The levels were not quantified.

Kutz, et al. (1978) analyzed 418 human urine samples collected from the general population via the Health and Nutritional Examination Survey. Residues of 2, 4, 5-trichlorophenol were found in 1.7 percent of the samples. The average level found was less than 5 µg/l (ppb) and the maximum value found was 32.4 µg/l.

Assuming that the exposure to chlorophenol is steady-state, that 100 percent of absorbed chlorophenol is excreted in the urine, and that the average urine void is 1.4 l/day per 70 kg person, initial exposure levels can be estimated from residual levels found in the urine. For example, the exposure level leading to the 5 µg/l residue can be calculated as follows:

$$\text{Exposure Level} = \frac{(5\ \mu g/l) + (1.4\ l/day)}{70\ kg} = 0.1\ \mu g/kg/day$$

A similar calculation using the maximum urine residue value observed by Kutz, et al. of 32.4 µg/l gives an exposure of 0.648 µg/kg/day.

Possible sources of exposure are discussed below.

Ingestion from Water

Piet and DeGrunt (1975) found unspecified isomers of trichlorophenols in surface waters in The Netherlands, in concentrations from 0.003-0.1 µg/l (ppb).

Phenols are known to occur naturally in the environment (Hoak, 1957). For example, some aquatic plants release sufficient phenol to establish water levels of 300-960 µg/l. Phenols are found in raw domestic sewage at levels of 70-100 µg/l. Complex phenols are at least partially released by bacterial action in sewage treatment trickling filters. The decomposition of surface vegetation such as oak leaves also releases phenol.

The association of bad taste or odor in tap water with chlorophenols has been of interest for a number of years. Hoak (1957) reviewed aspects of this problem. Some chlorophenols have odor thresholds in the ppb concentration range. The addition of 0.2-0.7 ppm chlorine to water containing 100 ppb phenol results in the development of a chlorophenol taste. Increasing the level of chlorine or increasing the reaction time reduces the taste. Odor thresholds for chlorophenols in water are shown in Table 2

Burttschell, et al. (1959) proposed a mechanism for the chlorination of phenol in water. According to their scheme 2- and 4-chlorophenol are formed early. These molecules are further chlorinated to 2, 6- or 2, 4-dichlorophenol. The final product is 2, 4, 6-trichlorophenol. After 18 hours of reaction, the chlorophenol products in Burttschell's

TABLE 2

Comparison of Odor Thresholds for Chrolophenols in Water

	Threshold-µg/l	Reference
2-chlorophenol	0.33 (30°C.)	1
	2 (25°C.)	2
3-chorophenol	200 (30°.)	1
4-chlorophenol	33 (30°C.)	1
	250 (25°C.)	2
2,4-dichloropehnol	0.65 (30°C.)	1
	2 (25°C.)	2
2,5 dichlorophenol	3.3 (30°C.)	1
2,6-dichlorophenol	3 (25°C.)	2
2,4,5-tricholorphenol	11 (25°C.)	1
2,4,6-trichlorophenol	100 (30°C.)	1
	1000 (25°C.)	2
2,3,4,6-tetrachlorophenol	915 (30°C.)	1

References:

1. Hoak, 1957
2. Burttschell, et al. 1959

study consisted of less than 5 percent each 2- and 4-chloropehnol, 25 percent of 2, 6-dichlorophenol, 20 percent 2, 4-dichlorophenol and 40 to 50 percent 2, 4, 6-trichlorophenol.

Ingestion from Foods

One possible source of trichlorophenol exposure for humans is through the food chain, as a result of the ingestion by grazing animals of the chlorophenoxy acid herbicides 2, 4, 5-T (2, 4, 5-trichlorophenoxyacetic acid) or silvex (2-(2, 4, 5-trichlorophenoxy)-propionic acid). Residues of the herbicides on sprayed forage are estimated to be in the range of 100-300 ppm. In view of this, Clark, et al. (1976) fed cattle silvex at levels of 300, 1000 and 2000 ppm in the diet for 28 days, and fed sheep 2, 4, 5-T or silvex at 2000 ppm in the diet for 28 days. Based on feed consumption, the exposures are equivalent to 9 mg/kg (300 ppm), 30 mg/kg(1000 ppm) and 60 mg/kg (2000 ppm). Some animals were fed a clean diet during a seven day withdrawal before tissue samples were obtained. Muscle, fat, liver and kidney were analyzed for 2, 4, 5 trichlorophenol. In the sheep fed 2000 ppm 2, 4, 5-T and killed at the end of the 28 day feeding period, the 2, 4, 5-trichlorophenol residues were 0.13 ppm in muscle,less than 0.05 ppm in fat, 6.1 ppm in liver, and 0.9 ppm in kidney. Sheep held for the seven day withdrawal had 2, 4, 5-trichlorophenol residues of 4.4 ppm in liver and 0.81 ppm in kidney, and less than 0.05 ppm in fat and muscle. Levels of the 2, 4, 5-T herbicide at the end of 28 days ranged from 0.27 ppm in fat to 27 ppm in kidney. In sheep and cattle fed 2000 ppm of silvex, 2, 4, 5-trichlorophenol was not detected in muscle or fat at the end of 28 days. Residues in the liver were 0.2-0.5 ppm and in kidney were 0.1-0.17 ppm.

Bjerke, et al. (1972) fed lactating cows the herbicide 2, 4, 5-T and analyzed the milk for trichlorophenol. At feeding levels of 100 ppm 2, 4, 5-T in the diet, an occasional residue of 0.06 ppm or less of trichlorophenol was isolated. At a feeding level of 1000 ppm 2, 4, 5-T in the diet, residues of 0.15-0.23 ppm trichlorophenol were found in milk and cream. Three days after 2, 4, 5-T feeding at the 1000 ppm level was stopped, trichlorophenol residues in milk and cream were below detection limits of 0.05 ppm. Acid hydrolysis of milk samples indicated that there was no binding of the trichlorophenol.

Wright, et al. (1970) found that sheep metabolize the herbicide Erbon (2-(2, 4, 5-trichlorophenoxy)-ethyl 2, 2-dichloropropionate). Two metabolites were found in urine, (2-(2, 4, 5-trichlorophenoxy)-ethanol and 2, 4, 5-trichlorophenol). About 33 percent of the administered Erbon dose was eliminated as 2, 4, 5-trichlorophenol in urine in 96 hours. A dose of 100 mg Erbon/kg in sheep for seven days proved lethal. 2, 4, 5-Trichlorophenol residues in tissue were 0.21 ppm in brain, 5.54 ppm in kidney, 3.14 ppm in liver, 2.06 ppm in omental fat, and 1.00 ppm in muscle. Dosages of 50 mg Erbon/kg for 10 days followed by slaughter on day 11 resulted in no detectable 2, 4, 5-trichloro-phenol residues in tissues.

Stannard and Scotter (1977) from New Zealand determined the residues of various chlorophenols in dairy products following the use of chlorophenol containing dairy teat sprays, dairy soaps and antiseptics. The compound 3, 5-dimethyl-4-chlorophenol was shown to carry over into milk following application to the cow udder. While this particular compound is not of direct interest in this document, the possible mechanism of exposure deserves recognition.

Crosby and Wong (1973) found that 2, 4, 5-trichlorophenol is a photodecomposition product of the herbicide 2, 4, 5-T. About 38 percent of the 2, 4, 5-T was converted to the trichlorophenol.

Exposure to other chemicals could result in exposure to trichlorophenols via metabolic degradation of the parent compound. Kohli, et al. (1976) found that the major rabbit urinary metabolites of 1, 2, 4-trichlorobenzene were 2, 4, 5- and 2, 3, 5-trichlorophenol. 1, 2, 3-trichlorobenzene was metabolized to 2, 3, 4-trichlorophenol and smaller amounts of 2, 3, 6- and 3, 4, 5-trichlorophenol. 1, 3, 5-trichlorobenzene was metabolized to 2, 3, 5- and 2, 4, 6-trichlorophenol. The yields of metabolites ranged from 1 to 11 percent. Foster and Saha (1978) reported that chicken liver homogenates would metabolize lindane and the alpha and delta but not the beta isomers of 1, 2, 3, 4, 5, 6 hexachlorocyclohexane. The metabolic products included 2, 4, 6-trichlorophenol, and 2, 3-dichlorophenol, as well as di- and trichlorobenzenes. Tanaka, et al. (1977) found that isolated rat liver microsomes metabolized the alpha, beta, gamma, delta and epsilon isomers of benzene hexachloride (BHC) to 2, 4, 6-trichlorophenol.

Shafik, et al. (1972) showed that in one to two days, 30-50 percent of the insecticide Ronnel (0, 0-dimethyl 0-(2, 4, 5-trichlorophenyl) phosphorothioate) was excreted in the urine of rats as 2, 4, 5-trichlorophenol.

Even plants can metabolize another chemical to form a trichlorophenol metabolite. Moza, et al. (1974) demonstrated that corn and pea plants could metabolize pentachlorocyclohexene to the 2, 4, 6-, 2, 3, 5- and 3, 4, 6-trichloropehnol isomers.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for any of the following compounds, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith et al. Manuscript) to estimate the BCF for aquatic organisms that contain about eight percent lipids from the octanol-water partition coefficient (P). An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for the edible portion of all aquatic organisms consumed by Americans can be calculated.

Compound	P	BCF	Weighted BCF
2,4,5-trichlorophenol	6,000	440	130
2,4,6-trichlorophenol	4,900	380	110

Inhalation

No quantitative data on inhalation studies were found. From Table 1 it is noted that the vapor pressures of 2, 4, 5- and 2, 4, 6-trichlorophenol are about 1 mmHg at 72-76 degrees C. Consequently the trichlorophenols can be expected to vaporize to some extent.

Olie, et al. (1977) reported finding di-, tri- and tetrachlorophenols in flue gas condensates from municipal incinerators. The levels were not quantified.

Dermal

Roberts, et al. (1977) used human autopsy skin epidermal membranes in an *in vitro* test system to determine the permeability of human skin to various chemicals. 2, 4, 6-Trichlorophenol permeated the skin membrane and did not cause damage when tested at the maximum aqueous solubility of 0.09 percent (w/v) concentration.

PHARMACOKINETICS

Absorption, Distribution, and Metabolism

No data were available regarding these processes.

Excretion

2, 4, 5-Trichlorophenol is cleared rapidly from blood. Wright, et al. (1970) dosed sheep with Erbon, an herbicide that is metabolized to 2, 4, 5-trichlorophenol, and observed the disappearance of 2, 4, 5-trichlorophenol from the blood. An approximate blood half-life of 20 hours was estimated from the graphed data.

Another study showed the rapid clearance of 2, 4, 6-trichlorophenol, predominantly in urine. Korte, et al. (1978) administered 1 ppm 2, 4, 6-trichlorophenol in the diet to rats for three days and then studied elimination. Eighty-two (82) percent of the dose was eliminated in the urine and 22 percent in the feces. Radio-labelled trichlorophenol was not detected in liver, lung or fat obtained five days after the last dose.

EFFECTS

Acute, Sub-acute, and Chronic Toxicology

Table 3 presents data regarding acute toxicity of several trichloropehnol isomers. Differences in observed LD_{50}'s may be due to the use of different solvents.

The clinical signs of acute poisoning with 2, 4, 5-trichlorophenol include decreased activity and motor weakness (Deichmann, 1943). Convulsive seizures occur but are not as severe as with the monochlorophenols. The monochlorophenols with a pk_a of eight or higher are convulsants. At body pH (7.0-7.4) these chloropehnols are mainly undissociated. The tri- and tetrachlorophenols have lower pk_a's and tend not to be convulsants, with the exception of 2, 4, 6-trichlorophenol.

Farquharson, et al. (1958) determined the LD_{50} of isomers of trichlorophenol (Table 3). 2, 4, 6-Trichlorophenol produced convulsions when injected intraperitoneally. The 2, 3, 6- isomer occasionally resulted in convulsions when dosed animals were handled. All of the trichlorophenol isomers (3, 4, 5-, 2, 4, 5-, 2, 4, 6- and 2, 3, 6-) elevated body temperature 0.5 degrees C. Onset of rigor mortis occurred within five minutes of death as compared to 50 minutes for controls. Rats dosed with 2, 3, 6-, 3, 4, 5- or 2, 4, 5-trichlorophenol developed hypotonia in the hind limbs two to three minutes after intraperitoneal injection. The hypotonia then spread to the forelimbs and neck. All of the trichloro-

TABLE 3

Acute Toxicity of Trichlorophenols

CHEMICAL	SOLVENT	SPECIES	TOXIC RESPONSE	REFERENCE
2,4,5-Trichlorophenol	fuel oil	rat	oral Ld_{50}=820 mg/kg	Deichmann & Mergard, 1948
	corn oil	rat	oral LD_{30}=2960 mg/kg	McCollister, et al. 1961
	fuel oil	rat	subcutaneous LD_{50}=2260 mg/kg	Deichman & Mergard, 1948
	olive oil	rats	intraperitoneal LD_{50}=355 mg/kg	Farquharson, et al. 1958
3,4,5-Tricholorphenol	olive oil	rats	intraperitoneal LD_{50}=372 mg/kg	Farquharson, et al. 1958
2,4,6-Tricholorphenol	olive oil	rats	intraperitoneal LD_{50}=276 mg/kg	Farquharson, et al. 1958
2,3,6-Trichlorophenol	olive oil	rats	intraperitoneal LD_{50}=308 mg/kg	Farquharson, et al.1958

phenol isomers stimulated oxygen consumption of rat brain homogenate at concentrations of 5×10^{-5} to 10^{-3}M.

McCollister, et al. (1961) conducted a variety of toxicologic studies on 2, 4, 5-trichlorophenol in rats. The 2, 4, 5-trichlorophenol used in the acute studies was 97-98 percent pure; and, for the 90-day study, it was 99 percent pure. The acute oral LD_{50} was 2960 mg/kg.

Rabbits were given 28 daily oral doses of 2, 4, 5-trichlorophenol in 5 percent gum acacia solution (McCollister, et al, 1961). No effect was observed at doses of 1 or 10 mg/kg. At 100 mg/kg, slight renal pathology was reported. At 500 mg/kg, slight kidney and liver lesions were noted.

In rats, 18 daily doses of 1000 mg/kg during 24 days caused a transient weight loss that disappeared within 14 days (McCollister, et al. 1961). Dosages of 30, 100, 300 or 1000 mg/kg for 18 out of 24 days did not affect mortality, hematological variables (unspecified), blood urea nitrogen, final body weight or organ weight ratios. There were no microscopic lesions in lung, heart, liver, kidney, spleen, adrenal, pancreas or testes.

Rats in groups of 10 males and 10 females were fed 2, 4, 5-trichlorophenol at dietary levels of 100, 300, 1000, 3000 or 10,000 mg of trichlorophenol per kg of feed for 98 days (McCollister, et al. 1961). Assuming an average rat eats an amount of feed equivalent to 10 percent of its body weight each day, the equivalent doses are 10, 30, 100, 300 and 1000 mg/kg body weight.

Dosages of 100 mg/kg body weight or less produced no adverse effects as judged by behavior, mortality, food consumption, growth, terminal hematology, body and organ weights and gross microscopic pathology.

At 1000 mg/kg (10,000 mg/kg in diet), growth was slowed in females. There were no significant hematologic changes. Changes were noted in kidney and liver on histopathologic examination. The kidneys showed moderate degenerative changes in the convoluted tubular epithelium and early proliferation of interstitial tissue. The liver showed mild centrilobular degenerative changes characterized by cloudy swelling and occasional focal necrosis. There was slight proliferation of the bile ducts and early portal cirrhosis. The rats fed 300 mg/kg (3000 mg/kg feed) also showed histopathologic changes in kidney and liver that were milder than those observed in the higher dose. The histopathologic changes were considered to be reversible.

Anderson, et al. (1949) fed steers various levels of 2, 4, 5-trichlorphenyl acetate or zinc 2, 4, 5-trichlorophenate, as shown in Table 4. Feed consumption, daily weight gain, hemoglobin and packed cell volume were determined. The results are summarized in Table 5. Because of the limited number of animals per group, statistical analysis was not used. For day 154 there was only one control animal per compound. The authors concluded that the compounds were relatively nontoxic to the animals. Examination of Table 5 shows no clinically significant changes in hemoglobin or packed cell volume values. No gross lesions were observed at slaughter. The feed consumption data hint that with both compounds, the high dose groups were consuming less feed/kg/day. Tissues were not analyzed for the active agents.

Table 4

Design of Steer Feeding Study of Anderson, et al. (1949)

Group	N	Compound	Dose-mg/kg	Duration-days
1	2	zinc 2,4,5 trichlorophenate	0	--
2	2	"	17.64	78
3	2	"	52.92	154
4	2	"	158.77	78
5	2	2,4,5-trichlorophenyl acetate	0	---
6	2	"	17.64	78
7	2	"	52.92	154
8	2	"	158.77	78

Table 5

Average Results of Anderson, et al. (1949) Trichlorophenol Steer Feeding Study

Part 1: Results of feeding zinc 2,4,5-trichlorophenate

	Dose - mg/kg			
	0	17.64	52.92	158.77
Daily gain - 78 day (kg/day)	0.73	0.97	0.83	0.68
Daily gain - 154 day (kg/day)	0.77	--	0.71	--
Feed consumption				
gm/kg day^{-1}-78 day	35	32	33	24
gm/kg day^{-1}-154 day	30	--	37	--
Hemoglobin				
gm/100 ml -78 day	10.3	11.1	10.3	10.9
gm/100 ml -154 day	10.9	--	10.4	--
Packed cell volume				
PCV -78 day	34	37	34	37
PCV -154 day	36	--	35	--

Part 2: Results of feeding 2,4,5-trichlorophenyl acetate

	Dose - mg/kg			
	0	17.64	52.92	158.77
Daily gain kg/day 78 day	1.05	0.37	0.84	0.65
Daily gain kg/day -154 day	0.77	--	0.68	--
Feed consumption				
gm/kg-day^{-1} -78 day	36	37	37	30
gm/kg-day^{-1}-154 day	30	--	39	--
Hemoglobin				
gm/100 ml -78 day	9.1	12.1	11.1	11.7
gm/100 ml -154 day	--	--	11.3	--
Packed cell volume				
PCV -154 day	31	40	37	38
PCV -154 day	--	--	38	--

Tissue analyses showed an increase in zinc, but phenol was not detected. Meat prepared from the animals did not have any unusual taste or odor.

McCollister, et al. (1961) reported on skin irritation and sensitization studies in 200 humans. A five percent solution of 2, 4, 5-trichlorophenol in sesame oil was midly irritating in a few individuals upon prolonged contact, but there was no evidence of sensitization.

Bleiberg, et al. (1964) described various adverse health effects in 29 workers involved in the manufacture of 2, 4-D and 2, 4, 5-T. The workers had varying degrees of chloracne, hyperpigmentation and hirsutism. Eleven had elevated urinary uroporphyrins. Eleven of the 29 were diagnosed as having evidence of porphyria cutanea tarda, which is associated with liver dysfunction, porphyrinuria and bullous skin lesions. It is likely that some of these symptoms represent TCDD toxicosis.

Studies on the mechanism of action or subcellular effects of these compounds have primarily focused on effects on oxidative phosphorylation. Weinbach and Garbus (1965) tested the ability of various substituted phenols to completely uncouple oxidative phosphorylation in vitro. 2, 4, 5-Trichlorophenol caused complete uncoupling at 0.05 mM. The known uncoupler 2, 4-dinitrophenol completely uncoupled the test system at 0.1 mM for comparison. There was a positive relationship between mitochondria protein binding and uncoupling properties.

Parker (1958) studied the effect of chlorophenols on isolated rat liver mitochondria. 2, 4-Dinitrophenol was used as a reference compound because of its known ability to uncouple oxidative phosphorylation. An unspecified isomer of trichlorophenol, at 1.8×10^{-4}M, had 70 percent of the activity of 2.0×10^{-5}M of 2, 4-dinitrophenol. Mitsuda, et al. (1963) studied the effects of various chlorophenols on oxidative phosphorylation in isolated rat liver mitochondria. The test system used a 2.75 ml reaction medium at pH 7.0, containing 0.05 ml of mitochondrial suspension with 0.43 mg N. The concentration of chlorophenol required to produce a 50 percent inhibition in the production of ATP was determined (I_{50}). The I_{50} was 3 µM for 2, 4, 5-trichlorophenol and 18 µM for 2, 4, 6-trichlorophenol.

Stockdale and Selwyn (1971) reported that 2, 4, 6-trichlorophenol at 0.005 M resulted in 50 percent inhibition of lactate dehydrogenase, and that 0.0028 M resulted in 50 percent inhibition of hexokinase in vitro. Isolated ATPase was stimulated by 60 µM and inhibited by 1120 µM of 2, 4, 6-trichlorophenol.

Arrhenius, et al. (1977) studied the effects of chlorophenols on microsomal detoxication mechanisms using rat liver preparations. The experimental system examined the effects of the test chlorophenol on the microsomal metabolism of N, N-dimethylaniline (DMA) to formaldehyde and N-methylaniline (C-oxygenation) or to N, N-dimethylaniline-N-oride (N-oxygenation). In essence, the study examined disturbances in the detoxification electron transport chain. The concern as stated by Arrhenius, et al. was that compounds that could increase N-oxygenation could also influence the metabolism of other chemical toxicants, such as aromatic amines, which are formed by N-oxygenation. It is suggested that agents that increase N-oxygenation could be considered as synergists for the carcinogenic action of aromatic amines. A concentration greater than 1 mM of 2, 4, 6-trichlorophenol inhibits of C-oxygenation of DMA. A 3 mM concentration produces a small increase in N-oxygenation of DMA. In order to set this in a dose-response context, a concentration of 1 mM is equivalent to 197.46 mg trichlorophenol per 1 and 3 mM is equivalent to 592.38 mg/1.

Two studies have looked at the effect of trichlorophenol on the bio-chemistry of the lens portion of the eye. Korte, et al. (1976) showed that 10^{-3} M 2, 4, 5-trichlorophenol would reduce bovine lens content of ATP, ADP, glucose-6-phosphate and fructose following a 48-hour incubation. Levels of AMP and glucose were increased. Trichlorophenol decreased glucose-6-phosphate dehydrogenase activity but had no effect on lactate dehydrogenase, malate dehydrogenase, sorbitol dehydrogenase, fructose-1, 6-diphosphate aldolase or pyruvate kinase. Ismail, et al. (1975) showed that small amounts of 2, 4, 6-trichlorophenol would penetrate the rabbit eye. Small amounts of the chemical were placed in the eye and one hour later various parts of the eye were analyzed for the chemical. Highest amounts of the administered dose were found in the cornea (2.4 percent) and conjunctiva (2.49 percent). The aqueous and vitreous humor, lens, iris and choroid contained less than 0.17 percent each.

Synergism and/or Antagonism

No data were available.

Teratogenicity

No studies were found reporting on the presence or lack of teratogenic properites of trichlorophenols.

Mutagenicity

Fahrig, et al. (1978) found that 400 mg 2, 4, 6-trichlorophenol increased the mutation rate in a strain of Saccharomyces cerevisial. There was no effect on the rate of intragenic recombination.

In a mouse mammalian spot test females were treated with an intraperitoneal dose of test chemical on day 10 of gestation and the response was a change in hair coat color representing a genetic change in the offspring(Fahrig, 1978). At 50 mg/kg, 2, 4, 6-trichlorophenol produced two spots in two of 340 animals from 74 females. At 100 mg/kg there was one spot out of 175 mice from 42 females.

Rasanen, et al. (1977) tested chlorophenol for mutagenicity using the Salmonella-mammalian microsome Ames test with both the nonactivated and liver homogenate added systems. The following trichlorophenol isomers were tested and reported as non-mutagenic in both test systems: 2, 3, 5-, 2, 3, 6-, 2, 4, 5- and 2, 4, 6-trichlorophenol.

Carcinogenicity

Boutwell and Bosch (1959) conducted a series of experiments on the tumor promoting action of substituted phenols using repeated applications of concentrated solutions to the shaved backs of mice. The tumor initiator DMBA (9, 10-dimethyl-1, 2-benzanthracene) was used. A 20 percent solution of 2, 4, 6-trichlorophenol in benzene did not increase the incidence of papillomas in mice pretreated with the initiator DMBA. No carcinomas developed during the 15 week experiment. A 21 percent solution of 2, 4, 5-trichlorophenol in acetone increased the incidence of papillomas in mice pretreated with DMBA. Carcinomas did not develop during the 16-week experiment.

Innes, et al. (1969) dosed two strains of mice with 2, 4, 6-trichlorophenol for 18 months. Eighteen males (18) and 18 females of each strain were used, for a total of 72 animals. Beginning at seven days of age and continuing through 28 days, the mice were gavaged daily with the compound at 100 mg/kg. From one month to 18 months the mice were fed a diet containing 260 ppm, which resulted in an estimated exposure of 20-25 mg/kg. The results were inconclusive. In this large study, which involved 120 pesticides, each chemical was grouped into one of three categories. If the incidence of tumors was significantly increased, it was classified as a carcinogen. If the incidence of tumors was low and statistically insignificant, it was classified as a non-carcinogen. The third category, in which 2, 4, 6-trichlorophenol was placed, comprised compounds requiring further study. The authors did not provide the actual data, but indicated that there was an elevation of tumor incidence in an uncertain range, and that additional statistical evaluation or experimentation would be required before an interpretation could be made.

CRITERION FORMULATION

The information of this section is presented in a composite treatment of the chlorophenols at the end of the document.

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TETRACHLOROPHENOL

Mammalian Toxicology and Human Health Effects

SUMMARY

Tetrachlorophenol is a fungicide and wood preservative. It is used as a water soluble salt to treat freshly cut lumber with either a spray or dip treatment. The treatment prevents sap stain organisms from growing in wood while it is drying or waiting further processing.

Commercial pentachlorophenol contains three to ten percent tetrachlorophenol (Goldstein, et al., 1977; Schwetz, et al., 1978). The annual production of 25 million kg of pentachlorophenol means that 0.75-2.5 million kg of tetrachlorophenol are produced concurrently and end up in the same places as pentachlorophenol.

There are three isomers of tetrachlorophenols the most important of which is 2,3,4,6-tetrachlorophenol. Table 1 lists the physiochemical properties of the three isomers.

Like tri- and pentachlorophenols, tetrachlorophenol contains toxic non-phenolic impurities. Schwetz, et al. (1974) reported that commercial grade 2,3,4,6-tetrachlorophenol contained chlorodioxin isomers at levels of 28 ppm (hexa-), 80 ppm (hepta-), and 30 ppm (octachlorodibenzo-p-dioxin) as well as chlorodibenzofurans at levels of 55 ppm (hexa-), 100 ppm (hepta-) and 25 ppm (octachlorodibenzofuran). The commercial tetrachlorophenol was composed of 73 percent tetra- and 27 percent pentachlorophenol.

TABLE 1

Physiochemical Properties of Tetrachlorophenol[a]

Property	Tetrachlorophenol Isomer		
	2,3,4,5	2,3,4,6	2,3,5,6
Molecular weight	231.89	231.89	231.89
Formula	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$
Melting point °C	116-7	70	115
Boiling point °C	sublimes	sublimes	150
Density	-	-	-
Solubility			
water	-	slightly	slightly
alcohol	very	soluble	-
ether	-	-	-
acetone	-	-	-
benzene	-	soluble	very
Vapor pressure-mm Hg (pressure, °C)	1mm, 100°	-	-
CAS Number*	N.L.[b]	000058902	N.D.[b]

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[a] Source: Handbook of Chemistry and Physics, 59th Edition, R.C. Weast, Editor, CRC Press, 1978.

[b] N.L. = not listed in toxic substances list
N.D. = listed in toxic substances list but no CAS number given.

EXPOSURE

Introduction

There is no direct evidence that the human population is being directly exposed to tetrachlorophenol. Residues have not been reported in foods nor have levels been reported in blood or urine. This lack of evidence reflects one of two possibilities. First, there may actually be little or no exposure. Second, exposure may be occurring without being discovered or quantified.

Ingestion from Water

There are reports suggesting the presence of lower chlorophenols occurring in drinking water, but the presence of tetrachlorophenol has not been documented. The odor threshold for 2,3,4,6-tetrachlorophenol in drinking water is 915 ppb at 30°C (Hoak, 1957).

Ingestion from Food

There is no evidence to suggest that tetrachlorophenols may be ingested from foods. If such compounds were in food, they could probably be absorbed from the gut.

One interesting problem associated with exposure of poultry to tetrachlorophenol-treated wood shavings has been the resulting musty taint that developed in meat and eggs. Parr, et al. (1974) conducted a small survey on the amount of tetra- and pentachlorophenol entering poultry housing as a result of using treated wood shavings. The problem developed when a musty taint was observed in broiler chickens. The musty taint was due to the fungal formation of tetra- and pentachloroanisoles formed by the methylation of the parent chlorophenol. The average 2,3,4,6-tetrachlorophenol level in fresh shavings was 54 µg/g (ppm). The spent litter contained 0.7 µg/g tetrachlorophenol and 0.5 µg/g tetrachloroanisole. The tetrachloroanisole was only occasionally detected in fresh shavings. For comparison, the fresh shavings contained an average of 12 µg/g of pentachlorophenol, and spent litter contained 0.02 µg/g of pentachloroanisole and 0.3 µg/g of pentachlorophenol. The odor threshold for 2,3,4,6-tetrachloroaniscle was reported to be 4 x 10-6 µg/g (4 ppt).

Harper and Balnove (1975) analyzed tissues from chickens raised in contact with tetrachlorophenol treated wood shavings. The levels of tetrachloroanisole in the chickens ranged from 1.2 ng/g in the edible portion to 7.6 ng/g in bone.

Engel, et al. (1966) fed 1 mg of 2,3,4,6-tetrachloroanisole/kg to chickens. A musty taint developed in eggs and broiler meat similar to that associated with keeping chickens on tetrachlorophenol treated wood shavings.

There is a possibility that the metabolism of other compounds could result in the formation of tetrachlorophenols. Engst, et al. (1976) reported that rats partially metabolized pentachlorophenol to 2,3,4,6- and 2,3,5,6-tetrachlorophenol. Ahlborg (1978) could not replicate the Engst results but rather found that rats metabolized pentachlorophenol to 2,3,5,6-tetrachlorohydroquinone and trichlorohydroquinone.

Kohli, et al. (1976) studied the metabolism of tetrachlorobenzene in rabbits. Both 1,2,3,4- and 1,2,3,5-tetrachlorobenzene were metabolized to 2,3,4,5- and 2,3,4,6-tetrachlorophenol. In addition, 1,2,3,5-tetrachlorobenzene resulted in 2,3,4,6-tetrachlorophenol. 1,2,4,5-Tetrachlorobenzene resulted in only one metabolite 2,3,5,6-tetrachlorophenol. All metabolites were isolated from urine.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans.

A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for any of the following compounds, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about eight percent lipids from the octanol-water partition coefficient (P). An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for the edible portion of all aquatic organisms consumed by Americans can be calculated.

Compound	P	BCF	Weighted BCF
2,3,4,6-tetrachlorophenol	20,000	1,100	320

Inhalation

Olie, et al. (1977) reported finding di-, tri-, and tetrachlorophenols in flue gas condensates from municipal incinerators. The levels were not quantified.

Dermal

No available data.

PHARMACOKINETICS

Absorption and Distribution

No available data.

Metabolism and Excretion

Ahlborg and Larsson (1978) studied the urinary metabolites of tetrachlorophenol in rats following intraperitoneal doses of 10 mg/kg. 2,3,5,6-tetrachlorophenol was excreted as unchanged tetrachlorophenol and as tetrachloro-p-hydroquinone. No trichloro-p-hydroquine was found in the urine of rats given the 2,3,5,6-tetrachlorophenol isomer. In a quantitative study rats were given 5.3 mg of 2,3,5,6-tetrachlorophenol, and the urine was collected for 24 hours. Over 98 percent of the administered dose was recovered in the urine in 24 hours, indicating an excretion half-life of less than one day. About 66 percent of the chlorophenol was excreted as unchanged 2,3,5,6-tetrachlorophenol and 35 percent was eliminated as tetrachloro-p-hydroquinone. After 24 hours neither parent compound nor metabolite could be found in the urine. This may indicate a one to two percent fecal excretion. The 2,3,4,5,- and 2,3,4,6 tetrachlorophenol isomers are not metabolized to any large extent. The 2,3,4,5-isomer is primarily excreted as unchanged chlorophenol with trace amounts of trichloro-p-hydroquinone appearing in the urine. Fifty-one percent of the administered dose was recovered in the urine in 24 hours. During the second 24 hours, an additional seven percent of the dose appeared in the urine. Altogether, 59 percent of the intraperitoneal dose was recovered in the urine with the disposition of the remainder of the dose not identified.

The 2,3,4,6-tetrachlorophenol isomer is rapidly eliminated in the urine as unchanged chlorophenol. About 94 percent of the intraperitoneal dose was recovered in the urine in 24 hours. Trace amounts of trichloro-p-hydroquinone were found in the urine. In the experiments of Alhborg and Larsson the urine was boiled in HCl to split any conjugates such as glucornides.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

The acute toxicity of tetrachlorophenol isomers via various routes and in several species is shown in Table 2. On an acute oral LD50 basis, tetrachlorophenol is less toxic than pentachlorophenol. In the studies of Ahlborg and Larsson (1978) pentachlorophenol had an oral LD50 of 150 mg/kg in mice and 294 mg/kg in gerbils. The comparative tetrachlorophenol LD50's ranged from 533 to 979 mg/kg. This point will be important in setting the criterion.

Tetrachlorophenol toxicosis consists of depressed activity and motor weakness (Deichmann, 1943). Tremors and convul-

TABLE 2

Acute Toxicity of Tetrachlorophenol and Metabolites.

CHEMICAL	SOLVENT	ANIMAL	TOXIC RESPONSE	REFERENCE
Tetrachlorophenol	fuel oil	rat	oral LD50 = 140 mg/kg	Deichmann, 1943
2,3,4,6-Tetrachlorophenol	propylene glycol	mouse, C57 female	oral LD50 = 150 mg/kg	Ahlborg and Larsson, 1978
	propylene glycol	gerbil, female	oral LD50 = 698 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 female	oral LD50 = 131 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 male	oral LD50 = 163 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 female	intraperitoneal LD50 = 82 mg/kg	Ahlborg and Larsson, 1978
	propylene glycol	mouse, C57 female	intraperitoneal LD50 = 121 mg/kg	Ahlborg and Larsson, 1978
Tetrachlorophenol	fuel oil	rat	subcutaneous LD50 = 210 mg/kg	Deichmann, 1943
	fuel oil	rat	subcutaneous LD50 = 200 mg/kg	Deichmann, 1943
2,3,5,6-Tetrachlorophenol	propylene glycol	mouse, C57 female	Oral LD50 = 543 mg/k	Ahlborg and Larsson, 1978
	propylene glycol	gerbil, C57, female	oral LD50 = 979 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 female	intraperitoneal LD50 = 48 mg/kg	Ahlborg and Larsson, 1978
	propylene glycol	mouse, C57 female	intraperitoneal LD50 = 109 mg/kg	Ahlborg and Larsson, 1978

CHEMICAL	SOLVENT	ANIMAL	TOXIC RESPONSE	REFERENCE
2,3,5,6-Tetrachlorophenol	ethanol	mouse, C57 female	oral LD50 = 109 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 male	oral LD50 = 89 mg/kg	Ahlborg and Larsson, 1978
2,3,4,5-Tetrachlorophenol	propylene glycol	mouse, C57 female	oral LD50 = 677 mg/kg	Ahlborg and Larsson, 1978
	propylene glycol	gerbil, female	oral LD50 = 533 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 female	oral LD50 = 400 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 male	oral LD50 = 572 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse; C57 female	intraperitoneal LD50 = 97 mg/kg	Ahlborg and Larrson, 1978
	propylene glycol	mouse, C57 female	intraperitoneal LD50 = 133 mg/kg	Ahlborg and Larsson, 1978
Tetrachloro-p-hydroquinone	ethanol	mouse, C57 female	oral LD50 = 500 mg/kg	Ahlborg and Larsson, 1978
Tetrachloropyrocatechol	ethanol	mouse, C57 female	oral LD50 = 612 mg/kg	Ahlborg and Larsson, 1978
Tetrachloro-p-hydroquinone	ethanol	mouse, C57 male	oral LD50 = 750 mg/kg	Ahlborg and Larsson, 1978
Tetrachloropyrocatechol	ethanol	mouse, C57 male	oral LD50 = 750 mg/kg	Ahlborg and Larsson, 1978

CHEMICAL	SOLVENT	ANIMAL	TOXIC RESPONSE	REFERENCE
Tetrachloro-p-hydroquinone	ethanol	mouse, C57 female	intreaperitoneal LD50 = 35 mg/kg	Ahlborg and Larsson, 1978
Tetrachloropyrocatechol	ethanol	mouse, C57 female	intraperitoneal LD50 = 136 mg/kg	Ahlborg and Larsson, 1978
Pentachlorophenol	propylene glycol	mouse, C57 female	oral LD50 = 150 mg/kg	Ahlborg and Larsson, 1978
	propylene glycol	gerbil, female	oral LD50 = 294 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 female	oral LD50 = 74 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 male	oral LD50 = 36 mg/kg	Ahlborg and Larsson, 1978
	ethanol	mouse, C57 female	intraperitoneal LD50 = 32 mg/kg	Ahlborg and Larsson, 1978
	propylene glycol	mouse, C57 female	intraperitoneal LD50 = 59 mg/kg	Ahlborg and Larsson, 1978

sions do not occur except in extremes.

Ahlborg and Larsson (1978) determined the acute oral and intraperitoneal LD50 of three isomers of tetrachlorophenol and related compounds in mice and gerbils (Table 2). The effect of solvent is shown by the increased toxicity of the chlorophenols when dissolved in ethanol versus propylene glycol.

Ahlborg and Larsson (1978) also determined the acute oral and intraperitoneal toxicity of tetrachloro-p-hydroquinone, which is the major urinary metabolite of 2,3,5,6-tetrachlorophenol in rats. When administered orally the metabolite was less toxic than any of the three tetrachlorophenol isomers in either male or female mice. However, when the metabolite was administered intraperitoneally in female mice it was more toxic than any of the three tetrachlorophenol isomers, and the LD 50 was similar to the intraperitoneal LD50 of pentachlorophenol (Table 2).

Farquharson, et al. (1958) showed that the intraperitoneal LD50 of 2,3,4,6-tetrachlorophenol in rats was 130 mg/kg. Convulsions did not occur, but there was a marked 4°C rise in body temperature, and rigor mortis occurred within five minutes of death. Brain homogenate oxygen consumption was stimulated at 5×10^{-5} M.

Schwetz, et al. (1974) reported that the ten day maximum tolerated dose for commercial 2,3,4,6-tetrachlorophenol in rats was 30 mg/kg day^{-1}. Deaths occurred in groups given 100 or 300 mg/kg day^{-1}.

Several investigators have examined the effect of tetrachlorophenol on cellular metabolism. Mitsuda, et al. (1963)

studied the effects of various chlorophenols on oxidative phosphorylation in isolated rat liver mitochondria. The test system used a 2.75 ml reaction medium at pH 7.0, containing 0.05 ml of mitochondrial suspension with 0.43 mg N. The concentration of chlorophenol required to produce a 50 percent inhibition in the production of ATP was determined (I_{50}). 2,3,4,6-Tetrachlorophenol had an I_{50} of 2 µM. For comparison, the I_{50} for pentachlorophenol was 1 µM and for 2,4-dinitrophenol the I_{50} was 17 µM.

Weinbach and Garbus (1965) tested the ability of various substituted phenols to completely uncouple oxidative phosphorylation *in vitro*. There was a positive relationship between mitrochondria protein binding and uncoupling properties. 2,3,4,6-Tetrachlorophenol caused complete uncoupling at 0.05 mM. For comparison, the known uncoupler 2,4-dinitrophenol completely uncoupled the test system at 0.1 mM.

Arrhenius, et al. (1977) studied the effects of chlorophenols on microsomal detoxication mechanisms using rat liver preparations. The experimental system examined the effects of the test chlorophenol on the microsomal metabolism of N, N-dimethylaniline (DMA) to formaldehyde and N-methylaniline (C-oxygenation) or to N, N-dimethylaniline-N-oxide (N-oxygenation). In summary, the study examined disturbances in the detoxification electron transport chain. The concern as stated by Arrhenius, et al. was that compounds that increased N-oxygenation could influence the metabolism of other chemical toxicants, such as aromatic amines, which are formed by N-oxygenation. Agents that increase N-oxygenation could be considered as synergists for the carcinogenic action of aromatic amines.

At a concentration greater than 0.3 mM, 2,3,4,6-tetrachlorophenol inhibits C-oxygenation of DMa and stimulates N-oxygenation of DMA. To help put this in a dose-response context, a concentration of 0.3 mM is equivalent to 69.57 mg of tetrachlorophenol/l.

Butler (1937) reported 21 cases of chloracne in workers handling a mixture of 2-chlorophenyl and tetrachlorophenol sodium.

Levin and Nilsson (1977) analyzed wood dust from sawmills in Sweden where chlorophenol fungicides are applied to green timber after sawing to prevent sapstain. The fungicide used consisted of 10 percent 2,4,6-trichlorophenol, 70 percent 2,3,4,6-tetrachlorophenol, and 20 percent pentachlorophenol, and contained 1600 ppm chlorophenoxyphenols, 70 ppm (Cl_6, Cl_7) chlorodibenzofurans, and less than 1 ppm chlorodibenzodioxins. The sawdust was obtained from the milling operations where the wood was trimmed after drying. The sawdust (four samples) contained 100-800 ppm 2,3,4,6-tetrachlorophenol, 30-400 ppm pentachlorophenol, 10-50 ppm chlorophenoxyphenols, 1-10 ppm chlorodibenzofurans and less than 0.5 ppm chlorodibenzodioxins. Occupational health problems such as severe skin irritation, respiratory difficulties and headache have been reported (Levin, et al. 1976). Sweden has banned the use of chlorophenols (Levin and Nilsson, 1977).

No toxicity studies of 90 days or longer were found. One long term study with pentachlorophenol is of some value in assessing the potential long term toxicity of tetrachlorophenol. Schwetz, et al. (1978) fed rats a low non-phenolic content commercial pentachlorophenol containing 10.4 ± 0.2 percent tetrachlorophenol and 90.4 ± 1.0 percent pentachlorophenol at levels of 1, 3, 10 or 30 mg/kg for 22 months (males) and 24 months (females). The results showed a no-observable effect level (NOEL) of 3 mg/kg (females) and 10 mg/kg (males) based on clinical chemistry, hematology, pathology and organ weight changes. This represents a tetrachlorophenol exposure of 0.312 mg/kg for females and 1.04 mg/kg for males.

Synergism and/or Antagonism

No data are available.

Teratogenicity

Schwetz, et al. (1974) administered commercial or purified tetrachlorophenol to rats on days six through 15 of gestation. Dosage levels used were 10 or 30 mg/kg. Neither grade of tetrachlorophenol was embryolethal or teratogenic. Both forms were fetotoxic at 30 mg/kg, with the effect being delayed ossification of the skull bones.

The only fetotoxic effect observed at 10 mg/kg was subcutaneous edema, which was not observed at 30 mg/kg. The non-phenolic impurities in commercial grade tetrachlorophenol did not alter the prenatal effects.

Mutagenicity

Rasanen, et al. (1977) tested chlorophenols for mutagenicity using the Salmonella-mammalian microsome Ames test with both the non-activated and liver homogenate added systems. 2,3,4,6-Tetrachlorophenol was reported as non-mutagenic in both test systems.

Carcinogenicity

No studies were found that were specifically designed to determine the carcinogenic properties of tetrachlorophenol. The study of Schwetz, et al. (1978) is of indirect value. This study is described in the effects section. The incidence of tumors is shown in Table 3. The authors concluded that low non-phenolic content pentachlorophenol containing 90.4 ± 1.0 percent pentachlorophenol and 10.4 ± 0.2 percent tetrachlorophenol was non-carcinogenic when tested at doses of 1, 3, 10 or 30 mg/kg in a rat life-time feeding study. The high dose represents a tetrachlorophenol exposure of 3.12 mg/kg.

While the data base is limited and less direct than desired, there is presently no indication that tetrachlorophenol is carcinogenic. The obvious long term consideration is the potential carcinogenicity of the chlorodibenzo-p-dioxins that may be present in commercial tetrachlorophenol.

TABLE 3

Incidence of Primary Tumors (Based on Histopathological Diagnosis) in Rats fed Pentachlorophenol (PCP) for 22 Months (Males) and 24 Months (Females) (Schwetz, et al. 1978)

	Males					Females				
Dose: mgPCP/kg/day	0	1	3	10	30	0	1	3	10	30
Number of rats examined:	27	26	27	27	27	27	27	27	27	27
Number of rats with tumors:	11	13	13	12	11	27	26	25	25	25
Number of tumors:	17	14	17	15	61	62	67	42	63	63
Number of tumors/rats with tumors:	1.6	1.1	1.3	1.4	2.3	2.6	1.7	1.7	2.5	2.5
Number of morphologic malignant tumors:	1	3	2	1	0	2	7	2	3	2

CRITERION FORMULATION

The information of this section is presented in a composite treatment of the chlorophenols at the end of the document.

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CHLOROCRESOLS

Mammalian Toxicology and Human Health Effects

SUMMARY

The chlorocresols structurally consist of a benzene ring with the substitution of one hydroxyl group, one methyl group and one or more chlorines. They are named either chlorocresols or chlorohydroxytoluenes. It is possible to have mono-, di-, tri- or tetrachlorocresols. Interestingly, no information was found on the chemical properties of trichlorocresols. Tables 1-3 list the physicochemical properties of the chlorocresols. The toxic substances list does not mention any of the chlorocresols, under either the cresol or hydroxytoluene names. Gosselin, et al. (1976) indicate that 6-chloro-m-cresol and p-chloro-m-cresol may be used as antiseptics and disinfectants. The United States Pharmacopeia does not list any of the chlorocresols. Goodman and Gilman (1975) do not discuss any of the chlorocresols. An unspecified isomer of chlorocresol has been used in England as a preservative in pharmaceuticals (Ainley, et al. 1977).

4-Chloro-m-cresol is a commercial microbicide marketed as Preventol CMK (Bayer) (Voets, et al. 1976).

Rapps (1933) found that p-chloro-m-cresol had antiseptic properties with a phenol coefficient of 13-25.

TABLE 1

Chemical Properties of Monochlorocresols.

Property	2-Chloro-p-cresol	6-Chloro-0-cresol	3-Chloro-0-cresol	4-Chloro-m-cresol	3-Chloro-p-cresol	2-Chloro-m-cresol
Molecular wt.	142.59	142.59	142.59	142.59	142.59	142.59
Formula	C_7H_7ClO	C_7H_7ClO	C_7H_7ClO	C_7H_7ClO	C_7H_7ClO	C_7H_7ClO
Melting point	---	---	86	66-8	55-6	55-6
Boiling point	195-6	188-9	225	235	228	196
Density	1.1785	---	---	---	---	---
Solubility						
water	slightly	---	slightly	slightly	soluble	slightly
alcohol	soluble	---	soluble	soluble	soluble	---
ether	soluble	soluble	soluble	soluble	soluble	---
acetone	---	---	---	---	---	---
benzene	soluble	---	soluble	---	soluble	---
Alternate name	3-chloro-4-hydroxy-toluene	3-chloro-2-hydroxy-toluene	2-chloro-6-hydroxy-toluene	2-chloro-5-hydroxy-toluene	2-chloro-4-hydroxy-toluene	2-chloro-3-hydroxy toluene

Source: Handbook of Chemistry and Physics, 59th Edition, R.C. Weast, Editor, CRC Press, 1978.

TABLE 2

Chemical Properties of Dichlorocresols.

Property	4,6-dichloro-m-cresol	2,6-dichloro-m-cresol	2,4-dichloro-m-cresol	4,6-dichloro-0-cresol	2,6-dichloro-p-cresol	4,5-dichloro 0-cresol
Molecular wt.	177.03	177.03	177.03	177.03	177.03	177.03
Formula	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$	$C_7H_6Cl_2O$
Melting point	72-4	58-9	27	55	39	101
Boiling point	235-6	236-6	241-242.5	266.5	138-9	---
Density	---	---	---	---	---	---
Solubility						
water	---	---	---	slightly	slightly	slightly
alcohol	---	---	---	very	soluble	soluble
ether	---	soluble	soluble	very	soluble	---
acetone	---	---	---	---	---	---
benzene	---	---	---	---	---	soluble
Alternate name	2,4-dichloro-5-hydroxy-toluene	2,4-dichloro-3-hydroxy-toluene	2,6-dichloro 3-hydroxy-toluene	3,5-dichloro-2-hydroxy-toluene	3,5-dichloro-4-hydroxy-toluene	4,5-dichloro 2-hydroxy-toluene

Source: Handbook of Chemistry and Physics, 59th Edition, R.C. Weast, Editor, CRC Press, 1978.

TABLE 3

Chemical Properties of Tetrachlorocresols.

Property	3,4,5,6-tetra-chloro-o-cresol	2,4,5,6-tetra-chloro-m-cresol	2,3,5,6-tetra-chloro-p-cresol
Molecule wt.	245.92	245.92	245.92
Formula	$C_7H_4Cl_4O$	$C_7H_4Cl_4O$	$C_7H_4Cl_4O$
Melting point	190	189-90	190
Boiling point	---	---	---
Density	---	---	---
Solubility			
water	---	---	---
alcohol	soluble	soluble	soluble
ether	soluble	soluble	---
acetone	---	soluble	---
benzene	soluble	soluble	soluble
Alternate name	2-hydroxy-3,4,5,6-tetrachlorotoluene	3-hydroxy-2,4,5,6-tetrachlorotoluene	4-hydroxy-2,3,5,6-tetrachlorotoluene

Source: Handbook of Chemistry and Physics, 59th Edition, R.C. Weast, Editor, CRC Press, 1978.

EXPOSURE

Introduction

In general, there are no published data available for the determination of current human exposure to chlorocresols. Although this fact may reflect an actual lack of exposure, it is also possible that exposures are simply going undetected and unquantified. Some studies have been done on the occurrence and use of chlorocresols.

An unspecified isomer of chlorocresol, assumed to be p-chloro-m-cresol, is used at a concentration of 0.15 percent to preserve mucous heparin in England (Ainley, et al. 1977). The intravenous use of this product in anticoagulation therapy results in human exposure. Heparin solutions marketed in the United States are preserved with benzl alcohol or thimerosal (Physicians Desk Reference).

The potential occurrence of chlorocresols in the environment was suggested by Jolley, et al. (1975) who reported 1.5 µg/l of 4-chloro-3-methylphenol (p-chloro-m-cresol) in chlorinated sewage treatment effluent. Another potential source is soil degradation of the hormone herbicide MCPA (4-chloro-2-methylphenoxyacetate). One metabolite of MCPA is 5-chloro-o-cresol (Gaunt and Evans, 1971). Rasanen, et al. (1977) found that technical MCPA contains 4 percent 4-chloro-0-cresol as an impurity.

Voets, et al. (1976) reported that p-chloro-m-cresol degraded 30 percent in two weeks in an aerobic minimal test and degraded 100 percent in two weeks in an aerobic activated sludge test system. There was no degradation in either test system under anaerobic conditions. In both series of tests the p-chloro-m-cresol concentration was 20 mg/l.

Ingestion from Water

No data are available.

Ingestion from Food

No data are available.

Inhalation

No data are available.

Dermal

No data are available.

PHARMACOKINETICS

Absorption

Roberts, et al. (1977) used human autopsy skin epidermal membranes in an in vitro test system to determine the permeability of chemicals through human skin. Chlorocresol, isomer not specified, permeated the membrane at a 0.4 percent (w/v) concentration after a 17 minute time lag. A concentration of 0.5 percent (w/v) damaged the membrane. Chlorocresol permeated more readily than either 2- or 4-chlorophenol but less readily than 2,4,6-trichlorophenol.

Distribution

No data are available.

Metabolism

No data are available.

Excretion

Zondek and Shapiro (1943) injected 1000 mg of p-chloro-m-cresol subcutaneously into a one kilogram rabbit. Not much detail was provided on effects other than that 15 to 20 percent of the dose was recovered in the urine. The same compound was given intramuscularly to humans and was not recovered in the urine to any appreciable extent. The dose was not specified but in a companion study 7 to 12 grams of p-chloro-m-xylenol was injected into humans.

EFFECTS

Acute, Sub-acute, and Chronic Toxicity

Von Oettingen (1949) reviewed the use and toxicity of the chlorocresols as part of an effort for the Experimental Biology and Medicine Institute, National Institutes of Health.

In 1939 Wien reported on acute toxicity studies with p-chloro-m-cresol. It was suggested that 0.3 to 0.25 percent p-chloro-m-cresol be used in place of 0.5 percent phenol for sterilization of solutions of thermolabile substances.

Tables 4 and 5 list the available toxicity data.

TABLE 4

Acute Toxicity of p-Chloro-m-cresol (Wien, 1939).

Animal	Route	Effect
Mouse	Subcutaneous	LD50 = 360 mg/kg
Mouse	Intravenous	LD50 = 70 mg/kg
Rat	Subcutaneous	LD50 = 400 mg/kg

TABLE 5

Acute Toxicity of Monochlorocresol (Schrotter, et al. 1977).

Chemical	Animal	Oral LD50
p-Chloro-o-cresol	mouse	1330 mg/kg
m-Chloro-o-cresol	mouse	710 mg/kg

Like the monochlorophenols, p-chloro-m-cresol produced severe muscle tremors and death in a few hours. Damage to renal tubules was noted at high dosages (Wien, 1939).

Wien also conducted some short term toxicity studies. A dose of 80 mg/kg given subcutaneously for 14 days did not adversely affect the growth of young rats. No lesions were found in kidney, liver, or spleen. Mild inflammation was reported at the injection site. Rabbits weighing 1.5 to 2.3 kg were injected subcutaneously with 12.5 mg p-chloro-m-cresol daily for four weeks. The dose represented 5 ml of a 1 in 400 solution, such as might be used to preserve a pharmaceutical. Only three experimental rabbits and no controls were used, making interpretation of the clinical data tenuous. No obvious changes were noted. Liver and kidney were normal histologically.

In the one report found on trichlorocresol (Eichholz and Wigand, 1931, cited by Von Oettingen, 1949), trichlorocresol, isomer not stated, was an effective intestinal antiseptic in a 0.25 percent solution. Rabbits tolerated 500 mg/kg oral doses for four consecutive days, but 600 mg/kg killed two of three rabbits. Clinical signs included convulsions.

Para-chloro-m-cresol has been reported to cause vesicular dermatitis in humans (Guy and Jacob, 1941). Concentrations of 1.5 percent (aqueous) cause a pruritic vesicular dermatitis in sensitive individuals. Symptoms occur in four hours and regress in a week.

Hancock and Naysmith (1975) reported two cases of generalized and seven cases of local reactions to mucous heparin preserved with 0.15 percent chlorocresol. The systemic reactions included collapse, pallor, sweating, hypotenion, tachycardia and generalized urticarial rash. Intradermal testing with chlorocresol-preserved heparin and non-chlorocresol heparin identified the cause to be the chlorocresol-preserved heparin.

Ainley, et al. (1977) also reported an adverse reaction involving heparin preserved with 0.15 percent chlorocresol. The reaction involved a local severe burning pain at the injection site that radiated up the arm. Shortly afterwards nausea and lightheadedness followed. The patient then became drowsy with pallor and sweating. Formal intradermal skin testing produced a reaction to the preserved heparin but not to the preservative-free heparin.

Synergism and/or Antagonism

No data are available.

Teratogenicity

No information was found reporting the presence or absence of teratogenic properties of any member of the chlorocresols group of chemicals.

Mutagenicity

Rasanen, et al. (1977) tested some chlorocresols for mutagenicity using the Salmonella-mammalian microsome Ames test with both the non-activated and liver homogenate added systems. The following chlorocresols were tested and reported as non-mutagenic in both test systems: 3-chloro-0-cresol, 4-chloro-0-cresol, and 5-chloro-0-cresol.

Carcinogenicity

No information was found reporting the presence or absence of carcinogenic properties of any member of the chlorocresols group of chemicals.

CRITERION FORMULATION

The information of this section is presented in a composite treatment of the chlorophenols at the end of the document.

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CRITERION FORMULATION

Existing Guidelines and Standards

No standards have yet been established for the monochlorophenols, dichlorophenols, tetrachlorophenols or chlorocresols.

No existing standards were found for the trichlorophenols; however, the National Academy of Sciences report Drinking Water and Health (1977) calculated a no-adverse-effect level of 0.7 mg 2,4,5-trichlorophenol/l based on the toxicity studies with that compound showing no-observable-effect levels (NOEL) of 10 mg/kg in dogs and mice and 30 mg/kg in rats. These levels were used to determine an ADI (acceptable daily intake) of 0.1 mg/kg.

Current Levels of Exposure

There are no available data for any of the chlorophenols on exposure levels.

Special Groups at Risk

There are no special groups at risk for the monochlorophenols, dichlorophenols, trichlorophenols or chlorocresols.

Special groups at risk for the tetrachlorophenols include manufacturers, users in wood sawmills, and wood treaters.

Basis and Derivation of Criteria

The chlorinated phenols which are the subject of this document are the monochlorophenols (3- and 4-chlorophenol); the dichlorophenols (2,5-; 2,6-; 2,3-; 4,6-; and 3,4-dichlorophenols) the trichlorophenols (2,4,5-; 3,4,5-; 2,4,6-; 2,3,4-; 2,3,5-; and 2,3,6-trichlorophenol) and the tetrachlorophenols (2,3,4,5-; 2,3,4,6-; and 2,3,5,6-tetrachlorophenols). In addition, the monochlorocresols are discussed.

Three chlorinated phenols have been the subject of separate criteria documents: 2-chlorophenol, 2,4-dichlorophenol and pentachlorophenol.

There are very little data on most of these compounds on chronic mammalian effects. However, the organoleptic effects of these compounds have been well documented (Table 1).

There are toxicity data on 2,4,5-trichlorophenol. McCollister, et al. (1961. Toxicol. Appl. Pharmacol. 3: 63) in 98 day feeding study on rats, demonstrated the No-Observable-Effect-Level (NOEL) for 2,4,5-trichlorophenol to be 100 mg/kg. Using the National Academy of Science's recommended uncertainty factor of 1000 (Drinking Water and Health, 1977) the Acceptable Daily Intake (ADI) is calculated to be 0.1 mg/kg of body weight, or 7 mg for a 70 kg person.

For the sake of establishing water quality criteria, it is assumed that on the average a person ingests 2 liters of water and 18.7 grams of fish. Since fish may bioaccumulate substances, a bioconcentration factor (BCF) is used in the calculation. The BCF for 2,4,5-trichlorophenol is 130 and was derived by U.S. EPA ecological laboratories in Duluth, Minnesota.

The equation for calculating an acceptable amount of 2,4,5-trichlorophenol in water based on the ingestion of 2 liters of drinking water and 18.7 grams of fish is:

$$(2\ \mathrm{l})\ x + (0.0187 \times F)\ x = \mathrm{ADI}$$

where

2 l = 2 liters of drinking water

0.0187 kg = amount of fish consumed daily

F = bioconcentration factor
(130 for 2,4,5-trichlorophenol)

ADI = Allowable Daily Intake
(mg/day for a 70 kg person)

$$(2\ l)\ x + (0.0187 \times 130)\ x = 7.0 \text{ mg}$$

$$2\ x + 2.43\ x = 7.0$$

$$4.43\ x = 7.0$$

$$x = 1.6 \text{ mg/l}$$

There are no toxicity data for tetrachlorophenol, but because of the similarities between tetra- and penta- chlorophenol and the lower acute toxicity of tetrachlorophenol, it is reasonable to set the water criterion on the basis of the more extensive toxicologic data base for pentachlorophenol.

The criterion is established as follows. The no observable effect level (NOEL) for pentachlorophenol is 3 mg/kg. Since the chlorophenols are rapidly excreted by mammals, an uncertainty factor of 100 is used to establish the acccept-able human exposure of 0.03 mg/kg per day. A water intake of 2 l/day and an average body weight of 70 kg are assumed. The acceptable whole body exposure is then 70 kg times 0.03 mg/kg/day which equals 2.1 mg/day.

Assuming that the total exposure is from ingesting 2 liters of drinking water and 18.7 grams of fish, the calculation previously described is employed:

$$(2\ 1)\ x + (0.0187 \times 320) = 2.1\ \text{mg}$$

$$2X + 5.98X = 2.1\ \text{mg}$$

$$7.98x = 2.1\ \text{mg}$$

$$X = .263\ \text{mg}$$

Thus, for tetrachlorophenol, which is based on the use of chronic toxicologic data and an uncertainty factor of 100, the recommended criterion level 263 µg/l. Drinking water contributes 25 percent of the assumed exposure while eating contaminated fish products accounts for 75 percent. The criterion level can alternatively be expressed as 351 µg/lif exposure is assumed to be from the consumption of fish and shellfish products alone.

The organoleptic properties of the chlorinated phenols are well known. These compounds have been reported to impart a medicinal-like odor and taste to water and to the flesh of aquatic organisms raised on contaminated water. Summaries of the reported taste/odor threshold levels of various chlorophenols in water or in aquatic organisms are presented in Table 1 and Table 2, respectively.

Water quality criteria for 2-chlorophenol and 2,4-dichlorophenol based on organoleptic effects were published in FR 15946, 1979. These criteria of 0.3 µg/l and 0.5 µg/l, respectively, were derived from the data reported by Hoak (1957) and are based on the odor threshold of these compounds in water.

The criteria for various other mono-, di,- and trichlorophenols have been derived and are based on the lower of the odor threshold in water or the tainting threshold

TABLE 1

Comparison of Odor Thresholds for Chlorophenols in Water.

	Threshold-ppb (µg/l).	Reference[a]
2-chlorophenol	0.33 ppb - 30°	2
	2 ppb - 25°	3
	6 ppb - NS[b]	4
3-chlorophenol	200 ppb - 30°C	2
4-chlorophenol	33 ppb - 30°C	2
	250 ppb - 25°C	3
	900 - 1350 ppb	4
2,4-dichlorophenol	0.65 ppb - 30°C	2
	2 ppb - 25°C	3
2,5-dichlorophenol	3.3 ppb - 30°C	2
2,6-dichlorophenol	3 ppb - 25°C	3
2,4,5-trichlorophenol	11 ppb - 25°C	2
2,4,6-trichlorophenol	100 ppb - 30°C	2
	1000 ppb - 25°C	3
2,3,4,6-tetrachlorophenol	915 ppb - 30°C	2

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a) 2 - Hoak, R.D. 1957. The causes of tastes and odors in drinking water. Proc. 11th Industrial Waste Conf. 41: 229. Purdue U.

3 - Burttschell, R.H., et al. 1959. Chlorine derivatives of phenol causing taste and odor. Jour. A.N.W.A. 51, 205.

4 - Campbell, C.L. et.al. 1958. Effect of certain chemicals in water on the flavor of brewed coffee. Food Res. 23: 575.

TABLE 2

Summary of Theshold Concentrations of Chlorinated Phenols in Water That Causes Tainting of the Flesh of Aquatic Organsisms

Compound	Theshold (µg/l)	Reference[a]
2-chlorophenol	15.0	5
	15.0	6
3-chlorophenol	60.0	5
4-chlorophenol	60.0	5
	50.0	6
2,4-dichlorophenol	5.0	6
	10.0	7

a) 5 - Schulze, E. 1961. The effect of phenol-containing waste on the taste of fish. Int. Revue Ges. Hydrobiol. 46, No. 1, p.81

6 - Teal, J.L. 1959. The control of waste through fish taste. Presented to American Chemical Society, National Meeting.

7 - Shumway, D.L. 1966. Effect of effluents on flavor of salmon. Dept. Fisheries and Wildlife. Agri. Exper. Sta. Oregon State U.

in aquatic organisms.

Since the criterion derived for tetrachlorophenol based on its toxic effects is lower than that derived as a result of its organoleptic properties, the former criterion is recommended.

There are no available data on monochlorocresols upon which to base a criterion.

A summary of the recommended criteria is presented in Table 3.

TABLE 3

Recommended Water Quality Criteria

Compound	Criterion from Organoleptic Effects	Criterion from Toxicological Data
Monochlorophenols		
3-chlorophenol	50 µg/l	none
4-chlorophenol	30 µg/l	none
Dichlorophenols		
2,5-dichlorophenol	3.0 µg/l	none
2,6-dichlorophenol	3.0 µg/l	none
Trichlorophenols		
2,4,5-trichlorophenol	10 µg/l	1600 µg/l
2,4,6-trichlorophenol	100 µg/l	
Tetrachlorophenol*		
2,3,4,6-tetrachlorophenol	915 µg/l	263 µg/l
Chlorocresol		
Insufficient data on which to base a criterion		

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* The criterion will be based on toxicological effects